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The impact of genetic and environmental risk factors for schizophrenia on cortical brain structure

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Abstract

Introduction

It is now accepted that Schizophrenia, a neurodevelopmental disorder which affects around 1% of the population, is influenced by both genetic and environmental risk factors. Schizophrenia is evidenced as being heritable with twin-heritability estimates of around 80%. Recently, the disorder has been demonstrated to be polygenic in nature; many genetic variants with individually small effects contribute to the overall phenotypic variation. Furthermore, cannabis use, adverse events, urbanicity, obstetric complications and migration, are five environmental risk factors that have been evidenced as being associated with an increased risk of developing the disorder. Abnormalities in brain structure are also well evidenced in individuals with schizophrenia, in particular, reduced cortical thickness, volume and surface area have been linked to those with schizophrenia when compared to healthy controls. It has been posited that these cortical alterations may predate disorder onset, for example, disruptions in brain development may be a function of experiencing schizophrenia-associated genetic and environmental risk factors. However, the link between genes, environment and brain structure within schizophrenia remains unclear. In this thesis, we aimed to examine whether genetic and environmental risk factors for schizophrenia directly impact cortical brain structure.

Methods and Results

The current aims were assessed using measures of cortical thickness, volume and surface area, as defined by FreeSurfer, in three separate studies. Firstly, ANCOVA models were applied to a case-control sample, the Scottish Family Mental Health (SFMH) study, $n_{controls}/n_{patients}$ = 41/58) to determine whether PolyGenic Risk Scores for Schizophrenia (PGRS-SCZ) are associated with lower cortical thickness both globally and within regions of interest (frontal and temporal lobes) as well as to examine whether the effects of experiencing an accumulation of the five environmental risk factors (outlined above) is associated with greater cortical thinning (Chapter Two). The results indicated that an increased PGRS-SCZ

was related to lower, global cortical thickness in the whole sample and not a result of group differences. With regards to environmental effects, the more environmental risk factors experienced, the lower the cortical thickness, this was specific to the temporal lobe.

Secondly, to further investigate the link between environmental risk factors of schizophrenia, we focused on birth weight as a proxy for obstetric complications (Chapter Three). Linear mixed effects regression (LME) models were used to assess whether birth weight was associated with cortical thickness, surface area and volume in a UK Biobank (UKB) sample (*n* = 1,680). We then applied Mendelian Randomisation (MR) to determine if birth weight-associated genetic variants were causally related to cortical structure. The results in this chapter suggested that higher weight at birth was associated with larger cortical volumes and surface area, both globally and in several cortical sub-regions. In contrast, a negative association was found between birth weight and cortical thickness in the lateral occipital parcel. MR analysis suggested a causal link of birth weight, as indexed by genetic variants, and insular lobe cortical volume as well as surface area globally, in the insular lobe and in middle temporal, medial orbitofrontal and inferior frontal gyrus parcels.

Lastly, we tested whether the same association between PGRS-SCZ and cortical thickness (outlined in Chapter Two) could be replicated within a subset of UKB (Chapter Four). For this, we again utilised LME models using the second genetic data release of UKB (*n* = 2,864). We tested this globally, lobarly and within 27 bilateral cortical parcels for each of these parameters. We found a higher PGRS-SCZ to be associated with lower global cortical volume and thickness as well as insular lobe cortical thickness. To further test potential environmental influences (as outlined in Chapter Three) on these effects, we used a liner regression model to test for a relationship between PGRS-SCZ and birth weight as well as LME models to test for interactional effects. No relationship was found between PGRS-SCZ and birth weight nor were there any significant interactions found between PGRS-SCZ and birth weight on cortical structure

Conclusion

Together, these studies highlight the fact that both genetic and environmental risk factors for schizophrenia may, indeed, directly but differentially impact cortical brain structure. This information may help us to further understand the progression of the disorder but also, by identifying and addressing these risk factors early, we may be able to minimise the impact that the disorder can have on cortical brain structure; particularly in relation to potentially modifiable factors, such as birth weight. We also highlight the importance of using large samples and replications in order to examine such relationships.

Lay Summary

Schizophrenia is a major psychiatric disorder which affects around 1% of the population and is thought to be around 80% heritable. This disorder is characterised by a range of symptoms which can impact upon an array of behaviours such as; the way we think, our emotions and our perception. Perhaps the best-known symptom of schizophrenia is psychosis; where an individual may 'hear voices' or have delusions. Thus, (despite its low occurrence within the population) schizophrenia can have large detrimental impacts on lifestyle, is one of the most severe mental health disorders in terms of disability and can ultimately be a high global and economic burden. Despite the large amounts of research that have been conducted in relation to the symptoms of schizophrenia, we still know relatively little about a how a person develops the disorder.

Genetic risk is thought to contribute to the development of schizophrenia. More recently, researchers have found evidence to suggest that schizophrenia is polygenic in nature. This means there are many genetic variants, each with small effects, that contribute to the development of the illness. These genetic variants, both common and uncommon, have been identified more often in individuals who have schizophrenia compared to healthy controls therefore, it has been possible to develop a score (known as a PolyGenic Risk Score; PGRS) which can be used to distinguish between schizophrenia patients and controls in many samples. Using this information, we can also determine whether individuals who possess more of these genetic risk variants are more likely to demonstrate other symptoms or brain abnormalities. This information may, in turn, help us to determine whether these symptoms or abnormalities predate the disorder and thus, can potentially be prevented. However, these scores have not been thoroughly tested for associations with variations in cortical brain structure.

Although these kinds of genetic advances will prove crucial in our ability to more accurately predict or diagnose this psychiatric disorder, an 80% heritability estimation suggests that

genetics alone cannot fully explain the cause of schizophrenia and thus, environmental factors must also be considered. Several environmental risk factors for schizophrenia have been identified. The most compelling evidence suggests that cannabis use, migration, growing up in an urban as opposed to rural environment, obstetric complications and experiencing adverse life events are all connected with an increased risk of schizophrenia. What remains unclear is whether these factors are directly associated with the cortical brain structure deficits that are also demonstrated in individuals with schizophrenia.

This thesis, examines the relationship between genetic and environmental risk factors for schizophrenia and how they impact cortical brain structure. Chapter Two suggests that both experiencing an accumulation of environmental risk factors and genetic risk factors for schizophrenia are directly associated with the thickness of the cortex (the distance between the white matter boundary and the brain surface) but in different ways. An increased genetic risk for schizophrenia was associated with global deficits in cortical thickness whereas, environmental risk factors impact more specific parts of the brain and only in patients.

Chapter Three examines associations between birth weight (a factor with both genetic and environmental components) and cortical thickness, surface area and volume. Birth weight was used as a proxy for the schizophrenia risk factor - obstetric complications. This chapter highlights that birth weight is, indeed, associated with all three of the tested cortical parameters, to varying degrees. After using a genetic analysis method to determine whether these associations between birth weight and cortical structure were causal, this chapter also suggests that there is indeed a causal link between birth weight, as measured using genetic variants, and several cortical volume and surface area regions.

In Chapter Four, we replicate the association between genetic risk for schizophrenia and cortical thickness (as outlined in Chapter Two), in a much larger sample (n = 2,864). We also found an additional effect whereby higher genetic loading for schizophrenia was related to lower insular lobe cortical thickness. The results in this chapter emphasise the need for ‘Big

Data' in order to find robust results. Furthermore, building upon findings from Chapter Three, we also tested whether consideration of birth weight would affect these results. However, we found no link between PGRS-SCZ and birth weight nor did we find any evidence of birth weight and PGRS-SCZ interactions within the aforementioned regions.

Together, these results suggest that both genetic and environmental risk factors for schizophrenia can impact upon brain structure, meaning that these factors may contribute to brain deficits associated with schizophrenia and may, potentially, predate the disorder. This information may help us to further understand the causation of the disorder but could also inform intervention; by identifying and addressing these risk factors early, we may be able to minimise potential damage to the brain in relation to schizophrenia, particularly when considering potentially modifiable risk factors such as birth weight.

Declaration

I hereby authorise the University of Edinburgh to publish the abstract of this thesis, and to authorise others to do so, for scholarly purposes and with proper acknowledgement of authorship.

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I declare that the work contained within this thesis has been composed by myself, and that, as part of a larger research group, I have properly acknowledged the contribution of others where appropriate. The contributions of both myself and co-authors has been explicitly detailed within the section **Publications,** below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others. I certify that this work has not been submitted for any other degree or professional qualification.

Signed: 

Emma Neilson

Date: 28/08/2018

Publications

A list of first-author publications that are based directly on the work constituting this thesis are presented below:

Chapter Two:

Neilson, E. N., Bois, C., Gibson, J., Duff, B., Watson, A., Roberts, N., Brandon, N. J., Dunlop, J., Hall, J., McIntosh, A. M., Whalley, H. C., Lawrie, S. M. (2017). Effects of environmental risks and polygenic loading for schizophrenia on cortical thickness. *Schizophrenia Research*, 184, 128-136, doi: 10.1016/j.schres.2016.12.011.

This study was conceived by EN, SML, AMM and HCW. EN wrote the manuscript text and prepared all tables and figures. SML was the main supervisor for the project, with co-supervision provided by AMM and HCW. EN performed manual edits on the MRI scans. CB aided in the statistical analysis. EMW and JG created the polygenic risk scores. EN and BD contributed to the data entry for the project. All authors reviewed the manuscript for publication.

Chapter Three:

Neilson, E., Shen, X., Clarke, T-K., Cox, SR., Wigmore, E. M., Gibson, J., Howard, D. M., Adams, M. J., Harris, M. A., Hagenaars, S., Davies, G., Deary, I. J., Boardman, J. P., Lawrie, S. M., McIntosh, A. M., Whalley, H. C. Assessing the causal impact of birth weight on cortical brain structure in UK Biobank. *In submission to International Journal of Epidemiology.*

This study was conceived by EN, SML, AMM and HCW. EN wrote the manuscript text and prepared all tables and figures. HCW was the main supervisor for the project, with co-supervision provided by TK-C, SML and AMM. EN, SX, SC and MAH performed quality control checks on all cortical imaging outputs. MJA created quality control pipelines for all other data. TK-C, DMH, and XS aided in the statistical analysis. All authors reviewed the manuscript for publication.

Chapter Four:

Neilson, E., Shen, X., Cox, S. R., Clarke, T-K., Wigmore, E. M., Gibson, J., Howard, D. M., Adams, M. J., Harris, M. A., Hagenaars, S., Davies, G., Deary, I. J., Whalley, H. C, McIntosh, A. M., Lawrie, S. M. Impact of polygenic risk for Schizophrenia on

cortical structure in UK Biobank (*n* = 2,864). *Under review at Biological Psychiatry;* https://www.biologicalpsychiatryjournal.com/article/S0006-3223(19)31283-1/fulltext

This study was conceived by EN, SML, AMM and HCW. EN wrote the manuscript text and prepared all tables and figures. SML was the main supervisor for the project, with co-supervision provided by HCW and AMM. EN, SC, and MAH performed quality control checks on all cortical imaging outputs. JG created the polygenic risk scores. MJA created quality control pipelines for all other data. XS aided in the statistical analysis. All authors reviewed the manuscript for publication.

To acknowledge the contributions of many co-authors, “we” will be used instead of “I” throughout this thesis. A complete list of publications (first- and co-author) received as part of this PhD are presented in **Appendix E** (p100-101).

Acknowledgements

First and foremost, I would like to acknowledge my supervisors Prof. Stephen Lawrie, Prof. Andrew McIntosh and Dr. Heather Whalley for giving me this opportunity and for their continuous help and advice throughout this project – your vast knowledge and expertise has been essential to my completion of this project and all of your time and effort has been greatly appreciated. I would like to give special thanks to my primary supervisor, Stephen Lawrie, for his guidance on all aspects of this thesis; his vision for the project, giving me the freedom to pursue the research I wanted, his help with editing all drafts of the thesis and, most importantly, his ability to help me re-focus when I became overwhelmed. In addition, I would like to thank Dr. Cathy Bois and Xueyi Shen for their unofficial supervision. Cathy, without your help in the beginning I think I would still be editing scans to this day; thank you for being there to answer all of my stupid questions and for making me laugh when I was close to tears. Shen, your support with R has helped me get through my mountain of analysis and your willingness to listen to my thought processes at different stages of the projects has been so helpful and very much appreciated. I could not have reached this stage without you both.

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Last, but not least, I would like to thank my Edinburgh family, the Doust's. Thank you for providing me with my home away from home and an escape from the city when I needed it. You were always there when I needed help or looking after, thank you!

List of Abbreviations

AE	Adverse events
ACC	Anterior cingulate cortex
ANCOVA	Analysis of covariance
AVENGEME	Additive Variance Explained and Number of Genetic Effects Method of Estimation
β	Beta (regression coefficient)
BD	Bipolar disorder
BW	Birth weight
CAE	Childhood adverse events
CI	95% confidence interval
CLEQ	Childhood life events questionnaire
CPZE	Chlopromazine equivalents
CRIC	Clinical research imaging centre
CT	Cortical thickness
CV	Cortical volume
DZ	Dizygotic
DLPFC	Dorso-lateral prefrontal cortex
ENIGMA	Enhancing neuroimaging genetics through meta-analysis
ERS	Environmental risk score
FA	Fully adjusted model
FDR	False discovery rate
Fig.	Figure
FUMA	Functional mapping and annotation of genetic associations
G×E	Gene × environment
GLM	General linear model
GWAS	Genome-wide association study
h^2	Twin heritability
HC	Healthy controls
HDRS	Hamilton depression rating scale
ICD	International classification of diseases
IDP	Imaging derived phenotype
IFG	Inferior frontal gyrus
IVW	Inverse variance weighted
IQ	Intelligence quotient
LD	Linkage disequilibrium
LME	Linear mixed effects
MDS	Multidimensional scaling component
MR	Mendelian randomisation
MRI	Magnetic resonance imaging
MZ	Monozygotic
NA	Not applicable - Unavailable participant information
NART IQ	National adult reading test intelligence quotient
OCs	Obstetric complications
OR	Odds ratios
p	Associated p-value of a test statistic
p_{corr}	FDR corrected p-value of a test statistic
PANSS	Positive and negative syndrome scale
PAT	Patient
PC	Principal component
PGC	Psychiatric genomics consortium
PGC-SCZ	Psychiatric genomics consortium schizophrenia

PGRS	Polygenic risk score
PGRS-SCZ	Polygenic risk score for schizophrenia
PRSice	‘Precise’ polygenic risk score software
R	Pearson’s correlation (coefficient)
R^2	Variance explained
RF	Risk factors
r_g	Genetic correlation
QC	Quality control
Q-Q	Quantile-Quantile
ROIs	Regions of interest
S.D	Standard deviation
S.E	Standard error
SA	Surface area
SCZ	Schizophrenia
SES	Socioeconomic status
SFMH	Scottish family mental health
SNPs	Single nucleotide polymorphisms
STG	Superior temporal gyrus
SWG-PGC	Schizophrenia working group of the Psychiatric Genomics Consortium
UKB	UK Biobank
X^2	Chi-squared (coefficient)
YMRS	Young mania rating scale

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Chapter One

Review of the Cortical Brain Structure Abnormalities Associated with Schizophrenia and Their Links with Polygenic and Environmental Risk Factors

1.1 Introduction

Schizophrenia is a chronic and debilitating psychiatric disorder which often manifests in adolescence or early adulthood (Bois et al., 2015a, Gogtay et al., 2011, Jablensky, 1997, Weinberger, 1987). Whilst the disorder is characterised by a multifaceted symptomatology, common symptoms include; positive symptoms (such as hallucinations, delusions and thought disorders), negative symptoms (such as social withdrawal and emotional blunting) (Picchioni and Murray, 2007) and cognitive impairments (Heinrichs, 2005). Schizophrenia is associated with an aberrant neurodevelopmental trajectory (Rapoport et al., 2012, Rapoport et al., 2005a, Weinberger, 1987) and poor prognosis (Volavka and Vevera, 2018, Bois et al., 2015a,) however, recent studies suggest that early detection and treatment, are associated with better clinical outcomes (Zipursky et al., 2018, Hegelstad et al., 2012, Lawrie et al., 2011, Henry et al., 2010). A recent paradigm shift from a neurodevelopmental perspective towards a 'Developmental Risk Factor Framework' places schizophrenia on the negative extreme of a psychosis spectrum on which risk factors can impact both before and after development (Murray et al., 2017). This framework suggests both that there are a range of risk factors that can be considered in relation to brain structure and that, based on an understanding of these, interventions could be successfully devised and applied at more than one developmental time point (Murray et al., 2017). However, further research is needed in order to help us fully understand the relationship between schizophrenia risk and cortical structure and is thus, the focus of the current thesis.

In utilising a range of neuroimaging and genetic methodologies, progress has been made in determining putative risk factors for the development of schizophrenia. To illustrate, family studies suggest the disorder is highly heritable (h^2 ~80%; Boos et al., 2007), with first- and second-generation relatives of individuals with schizophrenia having an increased chance of

developing it (Byun et al., 2012, Johnstone et al., 2005, Keshavan et al., 2004, Johnstone et al., 2000). Moreover, it involves numerous brain structure abnormalities which precede disorder onset, with evidence of further abnormalities as the disorder progresses (Boos et al., 2007). However, inconsistencies regarding the nature and timing of structural neuroimaging findings make it difficult to determine the underlying causes for cortical alterations (Bois et al., 2015a). A potential reason for this may be lack of consideration for environmental risk factors. Historically, researchers have found environmental causes for schizophrenia less compelling than genetic causes (Dean and Murray, 2005), although recent evidence suggests that environmental risk factors, as well as gene × environment (G×E) interactions, are important in schizophrenia aetiology (Murray et al., 2017, Karl and Arnold, 2014, Stepniak et al., 2014, Stilo and Murray, 2010, Dean and Murray, 2005). Thus, a more comprehensive investigation into how the interplay between genetic and environmental risk factors directly relate to cortical abnormalities in schizophrenia is still required.

The aim of this chapter is to provide a selective overview of current cortical structural imaging studies of schizophrenia, determine genetic and environmental risk factors identified for the disorder and, finally, outline how these factors may impact upon cortical structure. The importance of understanding the relationship between these three factors will be outlined, and how, in so doing, a more comprehensive understanding of the underlying causes of the disorder and potential interventions may be reached. This chapter will focus on cortical findings, from structural neuroimaging studies, associated with schizophrenia using three major cortical parameters; cortical volume (CV), thickness (CT) and surface area (SA). In addition, this chapter will outline the methodological considerations for employing both small case-control designs and large population-based cohorts to test for these relationships.

The three cortical parameters considered in this review are defined as follows: CT, thickness (mm) between the white matter and pial surface averaged over all vertices; SA (mm^2), the sum of the number of vertices in each region; and CV, which is a product of both SA and CT (mm^3) (Wierenga et al., 2014, Jalbrzikowski et al., 2013). See **Fig. 1.1.**

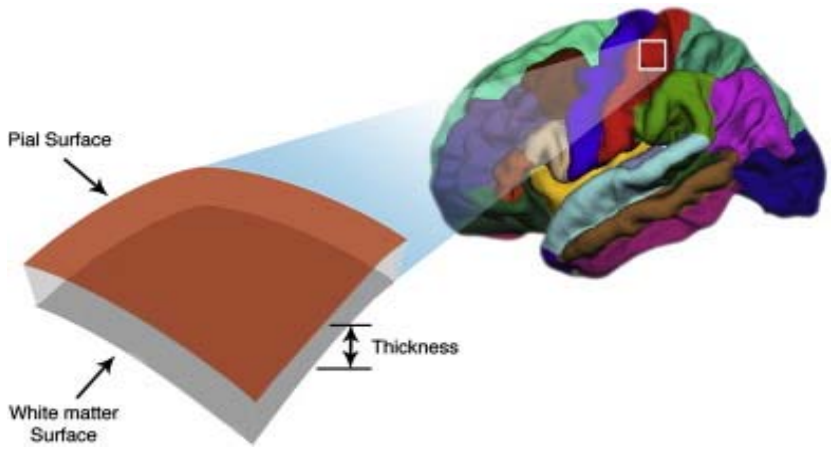

Fig. 1.1 Image demonstrating how cortical parameters CV, CT and SA are measured Image from (Wierenga et al., 2014)

The current review focuses on these three cortical metrics as they have been previously associated with cognitive functioning as well as a number of neurodevelopmental disorders, including schizophrenia, (Lee et al., 2016, Lyall et al., 2015). Furthermore, they have been previously asserted as appropriate metrics for investigation of the genetic relationship between schizophrenia and the brain (Lee et al., 2016). A vast amount of evidence suggests that variations in these cortical metrics are heritable; h^2 ranges from 66-97% for regional CV (Peper et al., 2007) and averages around 80% for global CV (Kremen et al., 2010, Wright et al., 2002), 81% for CT (Panizzon et al., 2009) and 89% for SA (Panizzon et al., 2009). However, the developmental trajectories of these measures are complex and not fully understood. It is established that CT and SA follow distinct, unique trajectories from both CV and each other (Wierenga et al., 2014). SA development peaks after CT but findings differ on the age in which this is achieved (Lyall et al., 2015, Wierenga et al., 2014, Shaw et al., 2012, Shaw et al., 2007). Despite the uncertainty of specific peak development timings, the most critical period for growth appears to be in the first two years of life, when all three parameters are highly susceptible to genetic and environmental insults (Lyall et al., 2015). Additionally, decreases with age in these three metrics have been reported in studies of adolescence (7-29 years) (Tamnes et al., 2017) and older age (18-87 years) (Lemaitre et al., 2012). CT has been linked with progressive neural changes from birth to adulthood, and CV and SA are associated with

the more rapid development occurring in early childhood (Lee et al., 2016). Therefore, investigating the associations between these three cortical structure metrics and the genetic and environmental risk factors for schizophrenia may be essential to fully understand the aetiology and development of schizophrenia.

1.2 Cortical Structure and Schizophrenia

1.2.1 Cortical Volume Regarding schizophrenia-associated abnormalities in cortical structure, CV (compared to CT and SA) has, historically, been the most studied cortical metric. Early reports describe decreased whole brain and hippocampal volume and increased lateral ventricles in schizophrenia (Harrisberger et al., 2016, Goldman et al., 2008, Shenton et al., 2001, Wright et al., 2000, Lawrie and Abukmeil, 1998) with more recent findings reporting widespread cortical volume reductions in patients compared to controls (Kong et al., 2015, Gupta et al., 2015, Rimol et al., 2012, Gutiérrez-Galve et al., 2010, Ellison-Wright and Bullmore, 2010, Goldman et al., 2008, Honea et al., 2008, Goghari et al., 2007, Honea et al., 2005), see **Table 1.1**.

Studies of unaffected relatives of individuals with schizophrenia have also been used to inform this relationship as they can help determine if structural differences can be linked with a genetic liability for the disorder, avoiding confounds such as secondary effects of illness or antipsychotic medication (Lawrie et al., 2001). Some of these familial studies have found smaller global and/or regional CV in healthy relatives of individuals with schizophrenia, when compared to controls (Boos et al., 2007, Goghari et al., 2007, Cannon et al., 2002a) whereas, other studies have found no significant differences (Goldman et al., 2008, Honea et al., 2008) despite finding a similar pattern of deficit in both disordered individuals and their relatives (Honea et al., 2008). However, these studies used voxel-based morphometry methods (see **Table 1.1**) which have been traditionally criticised for their sensitivity to image registration procedures (Voets et al., 2008). Furthermore, as CV is the product of CT and SA (Wierenga et al., 2014, Jalbrzikowski et al., 2013, Panizzon et al., 2009) investigation of all three of these metrics is required to reach a full understanding of the relationship between schizophrenia and cortical structure (Kong et al., 2015, Panizzon et al., 2009).

Table 1.1 A selective overview of results from relative and non-relative studies investigating the link between cortical volume and schizophrenia along with sample sizes and age ranges

Cortical Volume				
Author (Year of Publication)	**Study Type**	**Sample Size (Age Range, Mean, S.D)**	**Methodology**	**Result**
Gupta et al. (2015)	Mega-analysis	SCZ = 784 (18-64, NA, NA), HC = 936 (13-68, NA, NA)	SBM and VBM on GMC images	SCZ ↓ widespread GMC loss: most prominent in STG, inferior frontal gyrus and medial frontal cortex SCZ ↑ brain stem and cerebellum
Kong et al. (2015)	Meta-analysis	SCZ = 22 (NA, 53.95 ±8.53), HC = 20 (NA, 52.75 ±8.10)	VBM, SBM	SCZ ↓ widespread; most prominent in frontal and temporal regions but occipital and insular regions also involved
Ellison-Wright & Bullmore (2010)*	Meta-analysis	SCZ = 2,058 (NA, NA, NA) HC = 2,131 (NA, NA, NA)	VBM	SCZ ↓ GM in frontal, temporal, cingulate, insular cortex and thalamus SCZ ↑ basal ganglia
Wright et al. (2000)*	Meta-analysis	SCZ = 1,588 (NA), Comparison Subjects (related and non-related) = 1,783 (NA)	VBM/SBM	SCZ ↓ global cerebral volume and medial temporal lobe SCZ ↑ total ventricular volume
Rimol et al. (2012)	Cross-sectional	SCZ = 173 (NA, 32.3 ±9.0), HC = 207 (NA, 35.0, ±11.2)	SBM, FreeSurfer	SCZ ↓ widespread reductions in frontal, temporal, occipital and parietal regions
Crespo-Facorro et al. (2011)	Cross-sectional, Males only	SCZ (drug naive) = 26 (NA, 26.4 ±6.7), HC = 34 (NA, 25.2 ±6.2)	Manual trace	No differences in CV
Gutiérrez-Galve et al. (2010)	Cross-sectional	SCZ = 37 (16-49, 26.8 ±8.8), HC = 38 (16-37, 25.0 ±5.4)	SBM, FreeSurfer	No global differences in CV SCZ ↓ temporal lobe
RELATIVE STUDIES				
Boos et al. (2007)	Meta-analysis	SCZ = 679, (NA),	VBM/SBM	SCZ

		Relatives = 1,065 (NA), HC = 1,100 (NA)		Relatives ↓ total GM volume compared to HC
Ziermans et al. (2012)	Longitudinal	HR[ill] = 8 (NA, 16.8* ±2.2), HR[well] = 35 (NA, 15.3* ±2.1), HC = 30 (NA, 15.9* ±1.4)	SBM/VBM	No differences in total brain or GM
Brans et al. (2008)	Longitudinal, Twin Study	Discordant SCZ twin pairs – MZ SCZ = 9, MZ healthy = 9 (NA, 40.2 ±12.2), DZ SCZ = 10, DZ healthy = 10 (NA, 37.1 ±11.9), HC twin pairs – MZ 1 = 14, MZ 2 = 14 (NA, 35.5 ±11.8), DZ 1 = 13, DZ 2 = 13 (NA, 35.4 ±10.6)	SBM	SCZ and unaffected co-twins ↓ global, frontal and temporal lobe compared to HC
Goldman et al. (2008)	Cross-sectional	SCZ = 169 (17.83-61.63, 36.48 ±10.13), SIBS = 183 (17.37-58.25, 36.83 ±9.60), HC = 221 (18.39-60.86, 32.82 ±9.51),	VBM	SCZ ↓ global GM SCZ ↑ total ventricular volume No differences in SIBS compared to HC
Honea et al. (2008)	Cross-sectional	SCZ =169 (NA, 36.39 ±9.46), SIBS = 213 (NA, 36.5 ±9.75), HC =212 (NA, 33.1 ±9.86)	VBM	SCZ ↓ GM in frontal, temporal and parietal cortices compared to HC SIBS (nominal) ↓ medial frontal, STG and insular cortices
Goghari et al. (2007)	Cross-sectional	Relatives = 19 (NA, 34.1 ±8.4), HC = 22 (NA, 34.2 ±1.1)	SBM, FreeSurfer	Relatives ↑ left global Relatives ↓ right cingulate gyrus Relatives ↑ bilateral parahippocampal gyri, left middle temporal lobe

***** = studies defined as containing 'Big Data' (> 1,000 Smith & Nichols, 2018), **S.D =** standard deviation, **SCZ** = schizophrenia, **HC =** healthy controls, **SIBS** = healthy siblings of individuals with schizophrenia, **MZ** = monozygotic, **DZ =** dizygotic, **NA** = age range not documented, **VBM =** voxel-based morphometry, **SBM** = surface-based morphometry, **GM(C)** = grey matter (concentration), **STG** = superior temporal gyrus, **[a]** standard error reported rather than standard deviation

1.2.2 Cortical Thickness Lower CT in schizophrenia is associated with both specific brain regions (Kong et al., 2015, van Haren et al., 2011, Hartberg et al., 2011, Rimol et al., 2010, Fornito et al., 2008) and in widespread patterns across the cortex (Kong et al., 2015, Crespo-Facorro et al., 2011, Rimol et al., 2010, Yang et al., 2010, Goghari et al., 2007, Narr et al., 2005); resulting in global alterations. These deficits most consistently occur in the frontal and temporal lobes (Kong et al., 2015, van Haren et al., 2011, Rimol et al., 2010, Yang et al., 2010, Goldman et al., 2009, Nesvåg et al., 2008, Narr et al., 2005, Kuperberg et al., 2003). A similar pattern of results has also been evidenced in individuals at familial high-risk of schizophrenia when compared to healthy controls (Bois et al., 2015b, Byun et al., 2012, Jung et al., 2011, Goghari et al., 2007) and schizophrenia patients (Byun et al., 2012, Jung et al., 2011, Goldman et al., 2009), see **Table 1.2**.

Clinically, both the frontal and temporal lobes have been implicated in the emergence of psychotic symptoms. Specifically, cortical thinning in the middle and superior temporal gyri have been linked to the development of auditory verbal hallucinations (Cui et al., 2018, Oertel-Knöchel et al., 2013) and other positive symptoms (Walton et al., 2017), whereas lower CT in the frontal cortex has been related to negative symptoms (Walton et al., 2018) subjective cognitive dysfunction (Oertel-Knöchel et al., 2013) and disrupted verbal working memory (Guimond et al., 2016). Furthermore, there is evidence to suggest that these relationships are moderated by symptom severity (Guimond et al., 2016). As such, frontal and temporal CT could be particularly important neuroimaging markers upon which we could assess the potential impact of environmental risk factors for schizophrenia as well as measure the success of potential interventions.

Table 1.2 A selective overview of results from relative and non-relative studies investigating the link between cortical thickness and schizophrenia along with sample sizes and age ranges

Cortical Thickness				
Author (Year of Publication)	**Study Type**	**Sample Size (Age Range, Mean, S.D)**	**Method**	**Result**
Kong et al. (2015)	Meta-analysis	SCZ = 22 (NA, 53.95 ±8.53), HC = 20 (NA, 52.75 ±8.10)	VBM, SBM	SCZ ↓ widespread: including temporal, frontal insular and occipital regions
van Haren et al. (2011)	Longitudinal	SCZ = 96 (16.88-56.25, 32.22 ±11.10)*[1] HC = 113 (16.75-56.27, 35.28 ±12.25)*[1]	SBM	No global differences SCZ ↓left orbitofrontal, right STG and parahippocampal gyrus SCZ ↑ superior parietal lobule and occipital pole
Crespo-Facorro et al. (2011)	Cross-sectional, Males only	SCZ (drug naive) = 26 (NA, 26.4 ±6.7), HC = 34 (NA, 25.2 ±6.2)	SBM, Manual trace	SCZ ↓ global, frontal, temporal, parietal and occipital cortices
Hartberg et al. (2011)	Cross-sectional	SCZ = 117 (NA, 31.7 ±7.9), HC = 192 (NA, 36.1 ±9.6)	SBM, FreeSurfer	SCZ ↓ right caudal and rostral middle frontal and fusiform, left middle temporal
Gutiérrez-Galve et al. (2010)	Cross-sectional	SCZ = 37 (16-49, 26.8 ±8.8), HC = 38 (16-37, 25.0 ±5.4)	SBM, Freesurfer	No global differences SCZ ↓ right STG
Rimol et al. (2010)	Cross-sectional	SCZ = 173 (NA, 32.3 ±9.0), HC = 207 (NA, 36.2, ±9.7)	SBM, FreeSurfer	SCZ ↓widespread; most prominent in lateral and medial frontal lobes (including ACC) and temporal lobes
Fornito et al. (2008)	Cross-sectional	SCZ = 40 (NA, 22.29 ±3.22), HC = 40 (NA, 21.66 ±3.22)	SBM, FreeSurfer	SCZ ↓ ACC
Nesvåg et al. (2008)	Cross-sectional	SCZ = 96 (25-57, 42.1 ±7.3), HC = 107 (19-56, 41.6 ±9.0)	SBM, FreeSurfer	SCZ ↓ prefrontal and temporal cortex
Narr et al. (2005)	Cross-sectional	SCZ = 72 (NA, 25.1 ±4.7), HC = 78 (NA, 27.3 ±6.6)	SBM, manual trace	SCZ ↓supragenual anterior and posterior cingulate cortices and

				occipital regions in the medial cortex
Kuperberg et al. (2003)	Cross-sectional	SCZ = 32 (NA, 39 ±11), HC = 32 (NA, 40 ±10)	SBM, FreeSurfer	SCZ ↓ temporal and prefrontal lobes
RELATIVE STUDIES				
Bois et al (2015a)	Longitudinal	HR[ill] = 17 (16-23, 20 ±.40 [a]), HR[symp] = 57 (16-26, 21 ±.29 [a], HR[well] = 68 (16-27, 22 ±.2 [a]), HC = 36 (16-26, 21 ±.28 [a])	SBM, FreeSurfer	No global difference between all HR groups together and HC No global differences within the HR cohort
Sprooten et al. (2013)	Longitudinal	SCZ = 34 (NA, 21.59 ±3.63), HR = 144 (NA, 21.19, ±3.01), HC = 36 (NA, 21.17 ±2.37)	SBM, FreeSurfer	SCZ ↓ global: most prominent in frontal, parietal, supramarginal and lateral occipital cortices compared to HR and HC HR ↓left middle temporal cortex compared to HC
Ziermans et al. (2012)	Longitudinal	HR[ill] = 8 (NA, 16.8 ±2.2), HR[well] = 35 (NA, 15.3 ±2.1), HC = 30 (NA, 15.9 ±1.4)	SBM/VBM	HR[ill] ↓ widespread compared to HC including: ACC, precuneus, temporo-parieto-occipital regions HR[well] no differences compared to HC
Hedman et al. (2016)	Cross-sectional	Discordant SCZ twin pairs – MZ SCZ = 9, MZ healthy = 9 (NA, 40.2 ±12.2), DZ SCZ = 10, DZ healthy = 10 (NA, 37.1 ±11.9), HC twin pairs – MZ 1 = 14, MZ 2 = 14 (NA, 35.5 ±11.8), DZ 1 = 12 (NA, 34.0 ±9.9), DZ 2 = 12 (NA, 36.3 ±10.6)	SBM	Discordant SCZ twin pairs ↓ global and STG compared to HC
Byun et al. (2012)	Cross-sectional	SCZ = 31 (NA, 24.26 ±4.24), HR = 31 (NA, 22.61 ±5.47), HC = 29 (NA, 22.61 ±5.47)	SBM	SCZ ↓ widespread compared to HC, including: ACC, medial frontal, insula, temporal and parietal regions

				HR ↓ widespread compared to HC, including: frontal, temporal, parietal and occipital and ACC regions SCZ ↓ compared to HR: ACC, frontal and lateral orbitofrontal and anterior temporal regions SCZ ↑ compared to HR: occipital, medial and inferior temporal areas and orbitofrontal cortex
Jung et al. (2011)	Cross-sectional	SCZ = 31 (NA, 24.26 ±4.24), HR = 29 (NA, 22.24 ±4.33), HC = 29 (NA, 23.24 ±2.71)	SBM	SCZ ↓ widespread areas compared to HC including: superior frontal, inferior parietal and frontal, STG, ACC SCZ ↓ compared to HR, including: STG, superior and medial frontal, inferior temporal and parietal and ACC and insular regions HR ↓ widespread compared to HC, including: ACC, medial and inferior frontal prefrontal, STG and inferior parietal regions Gradual decreases could be found according to psychotic stages - HC > HR > SCZ
Yang et al. (2010)	Cross-sectional	SCZ = 48 (NA, 31.8 ±9.0), SCZ SIBS = 24 (NA, 31.8 ±13.3), SCZ parents = 42 (NA, 55.6 ±9.6), HC = 27 (NA, 26.4 ±7.1), HC SIBS = 38 (NA, 26.9 ±9.4), HC parents = 39 (NA, 56.1 ±8.0),	SBM	SCZ ↓total GM volume compared to HC SCZ ↓ global CT compared to HC SCZ ↓global CT compared to SCZ relatives SCZ relatives no difference in global CT compared to HC and HC relatives

Goldman et al. (2009)	Cross-sectional	SCZ = 115 (18.81-61.63, 37.39 ±10.46), SIBS = 192 (17.49-58.25, 37.49 ±9.77), HC = 196 (18.39-60.86, 33.51 ±9.67)	SBM	SCZ ↓ global compared to HC, most prominent: frontal lobe SCZ ↓ global compared to SIBS No differences in SIBS compared to HC
Goghari et al. (2007)	Cross-sectional	Relatives = 19 (NA, 34.1 ±8.4), HC = 22 (NA, 34.2 ±1.1)	SBM, FreeSurfer	No global differences Relatives ↓ bilateral cingulate lobe

S.D = standard deviation, **SCZ** = schizophrenia, **HC =** healthy controls, **SIBS** = healthy siblings of individuals with schizophrenia, **MZ** = monozygotic, **DZ =** dizygotic, **NA** = age range not documented, **VBM =** voxel-based morphometry,**SBM** = surface-based morphometry, **HR[ill]** = Individuals at familial high-risk (HR) who subsequently developed schizophrenia, **HR[symp]** = Individuals at familial high-risk (HR) who subsequently presented only isolated symptoms but were not diagnosed with schizophrenia, **HR[well]** = Individuals at familial high-risk (HR) who remained well, **ACC =** anterior cingulate cortex, **STG** = superior temporal gyrus, [a] standard error reported rather than standard deviation

1.2.3 Cortical Surface Area SA schizophrenia associations have received less empirical attention and existing studies report inconsistent findings (Gutiérrez-Galve et al., 2010). Whilst some evidence suggests cortical SA is lower in schizophrenia patients compared to controls both globally (Palaniyappan et al., 2011) and in specific regions (Rimol et al., 2012, Palaniyappan et al., 2011, Hartberg et al., 2011, Gutiérrez-Galve et al., 2010), others report SA to be higher (Bois et al., 2015b, Fornito et al., 2008) or no difference (Hedman et al., 2016, Crespo-Facorro et al., 2011) between these groups, see **Table 1.3**. Investigation into SA and genetic schizophrenia associations have been equally limited (Panizzon et al., 2009) and inconsistent. Lower cingulate and superior temporal SA, contrasting with increases in parahippocampal and middle temporal SA has been evidenced in unaffected relatives compared to controls (Goghari et al., 2007). Conversely, increased global, but not regional, SA has been reported in at-risk individuals (Bois et al., 2015b), although Hedman et al. (2016) provided no evidence of SA genetic liability. Further studies are required to fully explore the relationship between schizophrenia and SA and reach harmonious results.

Table 1.3 A selective overview of results from relative and non-relative studies investigating the link between cortical surface area and schizophrenia along with sample sizes and age ranges

Cortical Surface Area				
Author (Year of Publication)	**Study Type**	**Sample Size (Age Range, Mean, S.D)**	**Method**	**Result**
Rimol et al. (2012)	Cross-sectional	SCZ = 173 (NA, 32.3 ±9.0), HC = 207 (NA, 35.0, ±11.2)	SBM, FreeSurfer	SCZ ↓ some reductions in frontal, temporal, occipital and parietal regions
Crespo-Facorro et al. (2011)	Cross-sectional, Males only	SCZ (drug naive) = 26 (NA, 26.4 ±6.7), HC = 34 (NA, 25.2 ±6.2)	Manual trace	SCZ ↓ right straight gyrus and left orbitofrontal cortex
Hartberg et al. (2011)	Cross-sectional	SCZ = 117 (NA, 31.7 ±7.9), HC = 192 (NA, 36.1 ±9.6)	SBM, FreeSurfer	SCZ ↓ widespread frontal and temporal regions
Palinyappan et al. (2011)	Cross-sectional	SCZ = 57 (19-47, 26.10 ±7.49), HC = 41 (18-44, 28.04 ±6.63)	SBM, FreeSurfer	SCZ ↓ global particularly in several clusters of the left hemisphere
Gutiérrez-Galve et al. (2010)	Cross-sectional	SCZ = 37 (16-49, 26.8 ±8.8), HC = 38 (16-37, 25.0 ±5.4)	SBM, FreeSurfer	SCZ ↓ temporal lobe
Fornito et al. (2008)	Cross-sectional	SCZ = 40 (NA, 22.29 ±3.22), HC = 40 (NA, 21.66 ±3.22)	SBM, FreeSurfer	SCZ ↑ ACC
RELATIVE STUDIES				
Bois et al (2015a)	Longitudinal	HR[ill] = 17 (16-23, 20 ±.40 [a]), HR[symp] = 57 (16-26, 21 ±.29 [a],) HR[well] = 68 (16-27, 22 ±.25 [a]), HC = 36 (16-26, 21 ±.28 [a])	SBM, FreeSurfer	No difference between all HR groups together and HC HR[ill] ↑ global compared to HR[well] Trend ↑ HR[symp] global compared to HR[well]
Hedman et al. (2016)	Cross-sectional	Discordant SCZ twin pairs – MZ SCZ = 9, MZ healthy = 9 (NA, 40.2 ±12.2), DZ SCZ = 10, DZ healthy = 10 (NA, 37.1 ±11.9),	SBM	discordant SCZ twin pairs no global differences compared to HC

		HC twin pairs – MZ 1 = 14, MZ 2 = 14 (NA, 35.5 ±11.8), DZ 1 = 12 (NA, 34.0 ±9.9), DZ 2 = 12 (NA, 36.3 ±10.6)		
Goghari et al. (2007)	Cross-sectional	Relatives = 19 (NA, 34.1 ±8.4), HC = 22 (NA, 34.2 ±1.1)	SBM, FreeSurfer	Relatives ↑ left global Relatives ↓ right cingulate gyrus and STG Relatives ↑ bilateral parahippocampal gyri, left middle temporal lobe

S.D = standard deviation, **ACC** = anterior cingulate cortex, **SCZ** = schizophrenia, **HC =** healthy controls, **SIBS** = healthy siblings of individuals with schizophrenia, **MZ** = monozygotic, **DZ =** dizygotic, **NA** = age range not documented, **VBM =** voxel-based morphometry, **SBM** = surface-based morphometry, **HR[ill]** = Individuals at familial high-risk (HR) who subsequently developed schizophrenia, **HR[symp]** = Individuals at familial high-risk (HR) who subsequently presented only isolated symptoms but were not diagnosed with schizophrenia, **HR[well]** = Individuals at familial high-risk (HR) who remained well, **STG** = superior temporal gyrus, [a] standard error reported rather than standard deviation

Thus, current reports suggest that there is evidence of alterations in all three of these cortical metrics which can be linked to schizophrenia, most consistently for global, frontal and temporal CV and CT. Frontal and temporal CT in particular has been related to schizophrenia symptomatology and therefore may signpost a potential mechanism by which to explore schizophrenia risk. These regions will be given specific attention in Chapter Two. Furthermore, cortical alterations have been consistently evidenced in individuals at risk of developing schizophrenia and highlighted as potential, important markers for detecting susceptibility to the disorder (Bois et al., 2015a, Lawrie et al., 2011). Thus, suggesting that these metrics will also be suitable for exploring the relationship between cortical structure and genetic risk for schizophrenia.

1.3 Cortical Structure and Genetic High-Risk for Schizophrenia

Comparing individuals at genetic or familial high-risk for schizophrenia to those who have already developed it and healthy controls allows researchers to determine if there are schizophrenia-associated cortical alterations apparent before disorder onset and can aid in efforts to detect schizophrenia earlier (Bois et al., 2015a). Longitudinal studies have highlighted a similar pattern in CV and CT as cross-sectional results; decreased global, frontal and temporal CV in patients compared to controls (Brans et al., 2008) and, widespread cortical thinning in schizophrenia patients and familial high-risk groups compared to controls (Sprooten et al., 2013, Ziermans et al., 2012). However, Bois et al. (2015b) found no evidence of SA alterations in familial high-risk groups compared to healthy volunteers. This type of evidence suggests that cortical alterations associated with schizophrenia can become worse as symptoms develop and thus, highlight potentially important stages for interventions that could help to limit these cortical deficits. However, due to the limited number of studies and the relatively small sample sizes and heterogeneity associated with them (see **Tables 1.1-3),** further investigation is required before this type of information can be incorporated into a clinical framework (Bois et al., 2015a). Furthermore, these types of methods cannot be utilised at the population level and the results are therefore less generalisable.

1.3.1 Methodological Considerations

Neuroimaging samples are traditionally modest in size (n < 50; Smith and Nichols, 2018). In the literature referenced up to this point, sample cohort sizes range from 26 to 207 (excluding meta-analyses) with a mean of 91. Furthermore, family-based neuroimaging studies typically have even smaller sample sizes (current n range = 8-221, mean = 53), resulting from the necessity to investigate participants with familial relationships. However, the findings from these samples have been invaluable in developing our understanding of the cortical deficits associated with disorder and have the advantage of deep phenotyping (Gershon et al., 2018). Additionally, smaller samples are more practically achievable in terms of resources (e.g money, time, personnel, availability) (Monteith et al., 2015). But, being able to test these associations in larger samples, and with genetic instruments which require such sizes, would allow for opportunities to replicate findings as well as increase statistical power to detect smaller effects (Smith and Nichols, 2018). As such, both small and large sample studies are required and could be complimentary of one another.

Recently, efforts have been made to increase neuroimaging and genetics sample sizes using 'Big Data' (> 1,000) (Smith and Nichols, 2018). One approach is to use multi-site, world-wide collaborations. A recent case-control study by ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis: http://enigma.ini.usc.edu/), which included 4,474 individuals with schizophrenia and 5,098 healthy volunteers, found those with schizophrenia to have significantly thinner cortices (particularly in frontal and temporal regions) as well as lower global SA, when compared to controls (van Erp et al., 2018). Furthermore, van Erp et al. (2018) found these regional deficits to be associated with symptom severity. This publication offers evidence, from the largest cohort to date, and replicates the consistently reported finding of lower frontal and temporal CT in schizophrenia. However, an inevitable limitation of this approach is the inability to completely control for disparities in sample variables across sites, e.g. differences in scanners, recruitment methods, clinical assessments etc. (van Erp et al., 2018). Resources such as UK Biobank (UKB) will be necessary to fully control for such methodological issues.

UKB is a population-based sample which aims to collect 100,000 neuroimaging scans in individuals aged 40-69, utilising a single scanner and the same analysis pipeline (http://www.ukbiobank.ac.uk/). From the perspective of the current thesis, this sample will be useful in terms of identifying effects of risk factors for schizophrenia within the general population. Furthermore, as the 'Developmental Risk Factor Model' of psychosis suggests that the same factors which contribute to the risk of schizophrenia will also contribute to the potential risk of more minor symptoms in the general population (Murray et al., 2017), researchers could expect a similar effect on cortical structure. Currently available data from the UKB sample is thus analysed in the current thesis (Chapters Three and Four) in order to both, determine if replication of effects found using a case-control sample (Chapter One) can be achieved, and identify risk factors that may be neurodevelopmentally detrimental for the general population. Further reasons for analysing this UKB subset include; ability to avoid the mentioned confounds of meta-analysis research (e.g. scanner variations and recruitment inconsistencies) as well as the opportunity to test for cortical associations in an age range that is currently underrepresented in schizophrenia imaging research (Kong et al., 2015). However, when using a population-based sample, alternative methods will need to be utilised to determine the participants' genetic liability for schizophrenia. One such method is the recently developed PolyGenic Risk Scores (PGRS) (Dudbridge, 2013).

1.3.2 Polygenic Risk Scores for Schizophrenia

Genome Wide Association Studies (GWAS) have been utilised to identify disorder-associated genetic variants (SWG-PGC, 2014). GWAS have indicated that schizophrenia risk is likely determined by a large number of common allelic variations of small effect rather than specific susceptibility loci (Lee et al., 2012, Matheson et al., 2011, Gejman et al., 2010), which has led to the development of PGRS. To calculate PGRS for schizophrenia (PGRS-SCZ), schizophrenia-associated variants are first identified using a 'discovery' sample. The most recently conducted schizophrenia discovery GWAS identified 108 disorder-associated genetic

loci using 36,989 schizophrenia cases and 113,075 controls (SWG-PGC, 2014). These pre-identified variants are then found in an independent target sample, are weighted by their effect sizes in the discovery sample and summed across each individual genome (Dudbridge, 2013). PGRSs are thus used as a measure of genetic liability associated with a particular phenotype or disorder (Lewis and Vassos, 2017, Wray et al., 2014). For a PGRS-SCZ; the higher the PGRS-SCZ, the higher the risk of developing schizophrenia. These scores can, and are most commonly used, to predict case-control status in independent samples or to determine group differences in continuous phenotypes (Lewis and Vassos, 2017) but, they have some limitations. Firstly, the proportion of genetic variance explained by PGRS is relatively small (~2-3%) (Purcell et al., 2009), larger discovery and training samples could significantly increase the power of this method (Dudbridge, 2013). Secondly, the samples used to devise PGRS generally consist of participants with the same ethnic background (predominantly European) and thus may only be predictive in populations representing the same ethnicities (Warren, 2018). However, in their current state, PGRS-SCZ can also be applied to population-based samples, such as UKB (containing predominantly individuals with white-British ancestry), to infer genetic high-risk of the disorder which can result in increasing neuroimaging sample sizes. Furthermore, for the purposes of the current thesis, we can investigate the potential associations between these scores and cortical imaging measures.

1.3.3 Brain Structure and Polygenic Risk Scores for Schizophrenia

Only a small number of studies have been used to determine the relationship between PGRS-SCZ and brain structure phenotypes thus, some consideration will be given to subcortical and white matter volumes in the following section.

1.3.3.1 Cortical Volume Reus et al. (2017) found no associations between regional subcortical volume or white matter microstructure and PGRS-SCZ using the first data release of the UKB sample (n = 978). Importantly, this study did not examine cortical metrics as, at the time of analysis, the data release did not include these parameters. However, whilst higher PGRS-SCZ has been associated with lower global grey and/or white matter volume in some

smaller case-control studies (*n* cases = 24 and 152, controls = 38 and 142) (Oertel-Knöchel et al., 2015, Terwisscha van Scheltinga et al., 2013), analyses of healthy controls have failed to replicate a global effect (Lancaster et al., 2018, van der Auwera et al., 2015, Papiol et al., 2014) (*n* range = 197-763). These inconsistencies could be related to the varying sizes of both the discovery GWAS (SWG-PGC, 2014, SPGWASC, 2011) and target samples - it has been evidenced that the predictability of PGRS will be maximised as discovery and target sample sizes increase (Shen et al., 2017, Dima and Breen, 2015, Thompson et al., 2014, Lee et al., 2012) - as well as the use of different volumetric measures (e.g. total brain, white matter, intracranial volume). Study of regional differences in CV remain warranted, particularly in the general population (van der Auwera et al., 2015).

1.3.3.2 Cortical Thickness Using only healthy volunteers and splitting them into high (*n* = 98) and low (*n* = 99) PGRS groups, Lancaster et al. (2018) found no associations between PGRS group and average CT and only nominal regional associations in the superior parietal cortex and precuneus (Lancaster et al., 2018). However, the SNP inclusion threshold used in this publication ($P \leq 0.5$) is different to the one that will be tested in the current thesis ($P \leq 0.1$). Although the $P \leq 0.5$ threshold explained the most variance (schizophrenia liability) in the previous discovery GWAS (SPGWASC, 2011), the $P \leq 0.1$ threshold explains more variance in the most recent GWAS (SWG-PGC, 2014) and hence is implemented here, though other thresholds are detailed in the appendices. Furthermore, regardless of this methodological consideration, results from the volumetric studies highlight the importance of replicating such results.

1.3.3.3 Cortical Surface Area Lancaster et al. (2018) found no significant association between genetic loading for schizophrenia and global SA in healthy controls. No other studies investigating PGRS-SCZ and SA have currently been published.

Given the reported inconsistencies, and their limited number and heterogeneity, further studies are required to fully elucidate the relationship between PGRS-SCZ and cortical structure.

Chapter Two details a case-control investigation of this relationship between genetic loading for schizophrenia and cortical metrics and, in an effort to replicate any findings. Furthermore, investigating these relationships with larger sample sizes are required to increase the power of these findings, Chapter Four examines these within a larger general population-based cohort (UKB) study.

Although advances in genetic methodologies have enabled researchers to uncover genetic variants associated with schizophrenia and have helped to broaden our understanding of the role they play in its development and prognosis, genetics cannot fully explain the disorder. Twin concordance rates of schizophrenia are still only considered to be around 40-50% (Gejman et al., 2010) and no single gene with a large effect has been linked to the disorder. This suggests that investigating environmental risk factors for schizophrenia will be necessary for a full understanding of disorder development (Stilo et al., 2011, Dean and Murray, 2005).

1.4 Environmental Risk Factors for Schizophrenia

1.4.1 Epidemiological Evidence Schizophrenia has been associated with a number of both biological and social environmental risk factors. Cannabis use, obstetric/birth complications, urbanicity, migration and adverse life events are amongst the most commonly reported schizophrenia-associated environmental risk factors (Stilo and Murray, 2010, Dean and Murray, 2005, Mäki et al., 2005, Matheson et al., 2011, Sullivan, 2005, Stilo et al., 2011) and will therefore be the focus of the current overview.

1.4.1.1 Obstetric Complications Obstetric complications (OCs) are consistently associated with a greater incidence in people with schizophrenia (Forsyth et al., 2013, Clarke et al., 2006, Jablensky et al., 2005) as well as an increased risk for developing the disorder (pooled OR = 2) (Radua et al., 2018, Lærum et al., 2017, Rubio-Abadal et al., 2015, Forsyth et al., 2013, Cannon et al., 2002b, Geddes and Lawrie, 1995). Most commonly, the term OC includes three main categories; complications of pregnancy (e.g preeclampsia), abnormal

growth and development (e.g. low birth weight and reduced head size) and delivery complications (e.g. asphyxia and emergency Caesarean section) (Matheson et al., 2011, Stilo and Murray, 2010, Mäki et al., 2005, Cannon et al., 2002b, Geddes and Lawrie, 1995) (see **Fig. 1.2**). Season of birth, maternal exposure to illnesses such as influenza and diabetes and advanced paternal age at birth have also been consistently noted as risk factors (Stilo and Murray, 2010, Matheson et al., 2011, Mäki et al., 2005). All of these factors will be considered in the current thesis (see Chapter Two) as well as a more thorough investigation of birth weight in Chapters Three and Four.

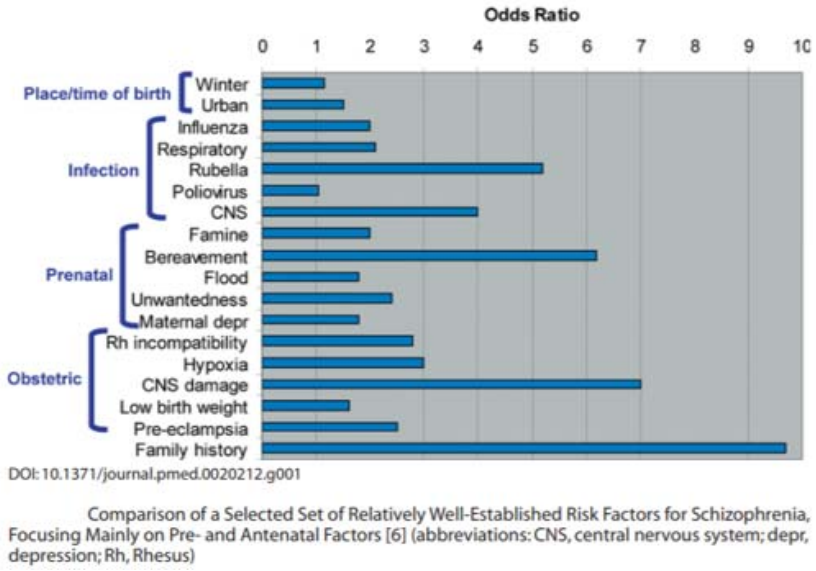

Fig. 1.2 Image showing a selection of obstetric risk factors for schizophrenia and their related odds ratios Image and legend from (Sullivan, 2005)

1.4.1.2 Adverse Events Adverse life events, particularly in childhood, have been consistently linked to schizophrenia and psychosis; childhood trauma is more commonly reported in schizophrenia patients than the general population and children who experience such trauma are at a greater risk of developing psychotic symptoms (Matheson et al., 2013, Schlosser et al., 2012, Dean and Murray, 2005). However, diverse understandings of what constitutes such an event have made it difficult to operationalise a definition and thus develop measures to test for its relationship with schizophrenia (Morgan and Fisher, 2007). As such, a range of childhood adverse events have been utilised and subsequently associated with

schizophrenia: bullying (Arseneault et al., 2010, Stilo and Murray, 2010, Schreier et al., 2009), parental loss/separation (Morgan et al., 2014, Stilo and Murray, 2010, Morgan et al., 2007), abuse (Radua et al., 2018, Schlosser et al., 2012, Stilo et al., 2011, Dean and Murray, 2005, Read et al., 2005), physical abuse (Stilo and Murray, 2010, Read et al., 2005), sexual abuse (Matheson et al., 2011, Chen et al., 2010, Read et al., 2005), emotional abuse/neglect (Read et al., 2005).

1.4.1.3 Cannabis Use Cannabis use has been consistently associated with an increased risk of schizophrenia (Dean and Murray, 2005, Arseneault et al., 2002), often in a dose-dependent manner (Manrique-Garcia et al., 2012, Mäki et al., 2005,). Cannabis is currently the most commonly used illicit drug in individuals aged 15 to 64 (UNODC, 2015), and as such, connotes a promising target for intervention at the population level (Murray et al., 2017, Stepniak et al., 2014, Mäki et al., 2005).

1.4.1.4 Urbanicity Higher incidence of schizophrenia and psychosis has been consistently associated with urban as opposed to rural areas (Haddad et al., 2015, Vassos et al., 2012, Dean and Murray, 2005, Freeman, 1994), with prospective studies suggesting a link between living in urban areas at birth or early childhood and the risk of developing the disorder (Dean and Murray, 2005). Furthermore, this risk may be increased by length of time spent in urban areas (Stilo and Murray, 2010, Dean and Murray, 2005, Pedersen and Mortensen, 2001). A recent systematic review identified urbanicity (and ethnic minority status) as a 'true risk factor' for schizophrenia (Radua et al., 2018, Kirkbride et al., 2017).

1.4.1.5 Migration Migration status has been consistently evidenced as one of the strongest risk factors for schizophrenia (Radua et al., 2018, Akdeniz et al., 2017), particularly in African-Caribbean migrants to England (Radua et al., 2018, Stilo and Murray, 2010). Such a finding has been reported in both first- and second-generation migrants (Akdeniz et al., 2017, Stilo and Murray, 2010, Dean and Murray, 2005).

In addition to their individual risk, recent evidence has also suggested that the accumulative effect of these environmental factors can be even more detrimental. Stepniak et al. (2014) reported an earlier onset age of up to nine years in individuals who experienced a higher number of environmental risks. Thus, consideration of the accumulative effect of the aforementioned risk factors on cortical structure may be just as important as testing them individually.

A point that is consistently made to promote the investigation of environmental risk factors for schizophrenia is that, unlike genetic variants, these are potentially modifiable and can aid in the development of preventative interventions (Tiemeier and Korevaar, 2016, McGrath and Lawlor, 2011, Stilo et al., 2011, Mäki et al., 2005). Furthermore, as schizophrenia is considered to have a neurodevelopmental component (Murray et al., 2017, Rapoport et al., 2012, Rapoport et al., 2005a, Weinberger, 1987), it is also important to understand if and how these risk factors may impact upon the brain as well as if preventative strategies can reduce these brain alterations. Thus, further consideration is needed of the link between these schizophrenia-associated environmental risk factors and cortical structure.

1.4.2 Cortical Structure and Environmental Risk Factors for Schizophrenia

1.4.2.1 Obstetric Complications Haukvik et al. (2009) tested for associations between number and severity of OCs and cortical thickness (CT) in patients and controls. Although CT differences were found between patients and controls, there was no evidence to suggest that these were related to OCs (Haukvik et al., 2009). Similar findings were reported by Smith et al. (2015) whilst investigating perinatal hypoxia and foetal growth (Smith et al., 2015). Foetal growth restriction has however, been associated with lower cortical volume (CV) (S. Miller et al., 2016, Smith et al., 2015) and surface area (SA) (Smith et al., 2015). Additionally, subtle differences in birth weight, even within those born at full-term, have been linked to lower CV, SA (Raznahan et al., 2012, Haukvik et al., 2014, Walhovd et al., 2012) and CT (Raznahan et al., 2012) in later life. However, lack of consistency and accuracy in some perinatal (for example) measures (Caughey, 2007) makes OC effects difficult to compare across studies.

1.4.2.2 Adverse Events Childhood adversity (defined by referral to the Children's Panel) has been related to significantly lower SA in the right hemisphere (Barker et al., 2016a). This same study found no effect for CT (Barker et al., 2016a). Habets et al. (2011) however, reported significantly lower CT in schizophrenia patients who experienced higher levels of developmental trauma (defined by the Childhood Trauma Questionnaire) (Bernstein et al., 1997) compared to controls. Inconsistencies in these results could be related to variability in adversity measures and much lower numbers of exposed compared to control individuals in the Barker et al. (2016a) study.

1.4.2.3 Cannabis Use In comparison to non- or occasional users, healthy, regular cannabis users have been found to have lower grey matter volume in temporal, hippocampal, insular and frontal regions (Battistella et al., 2014). Lower CT was found in schizophrenia patients who were users compared to those who were non-users (Habets et al., 2011). Furthermore, significant CT differences have been found between patients and controls, who use cannabis, in inferior frontal, occipital and parietal regions (Rais et al., 2010). This suggests that cannabis use impacts cortical structure regardless of schizophrenia risk. However, it has been suggested cannabis use may be more detrimental for those who go on to develop the disorder (Welch et al., 2011a).

1.4.2.4 Urbanicity and Migration Haddad et al. (2015) found lower CV in the dorso-lateral prefrontal cortex and the perigenual anterior cingulate cortex (ACC) for those who were born and raised in highly populated cities compared to those in rural or less populated areas. This perigenual ACC effect has also been replicated by Akdeniz et al. (2017) who, in addition, found the same region to be significantly lower in male (but not female) second-generation migrants. The authors assert that these effects could be related to social stress, defeat and discrimination impacting upon the brain at critical developmental periods (Akdeniz et al., 2017) and that they highlight 'potential mechanisms' for mental ill health (Haddad et al., 2015).

Such findings provide evidence for a strong environmental component impacting upon cortical structure in individuals at-risk for developing schizophrenia. However, these findings are limited by the strict focus on volumetric measures. It is important to note that neither environmental or genetic factors alone can fully explain schizophrenia aetiology or development (Stilo et al., 2011, Dean and Murray, 2005), nor can they always be so easily distinguished between. For example, birth weight is considered to have both genetic and environmental components (Gielen et al., 2008). Furthermore, some of the presented literature alludes to global cortical associations with PGRS and regional associations for some environmental factors however, overlaps, in frontal and temporal lobes in particular, are also evident in both relative and environmental risk studies. Consideration of G × E interactions are therefore necessary to fully develop the clinical picture of schizophrenia (Karl and Arnold, 2014, Dean and Murray, 2005).

1.5 Brain Structure and Interactions Between Genetic and Environmental Risk Factors for Schizophrenia

A G × E interaction is best defined as environmental factors exacerbating an individual's genetic predisposition to a given trait or disorder (Karl and Arnold, 2014, Tsuang et al., 2004). Although it is now widely accepted that testing of these interactions in schizophrenia studies is necessary (Karl and Arnold, 2014), its execution is not straight forward and a number of different methodological approaches have been considered (van Os et al., 2008). In relation to schizophrenia and neuroimaging markers, the majority of research has tested the association between cortical structure and the experience of environmental risk factors in individuals with a genetic vulnerability to schizophrenia (Geoffroy et al., 2013). Testing variations in neuroimaging phenotypes may help us to determine potential mechanisms for these G × E interactions (Geoffroy et al., 2013). Thus far, G × E interactions for schizophrenia and brain structure have been limited to investigation of OCs and cannabis use (Geoffroy et al., 2013).

1.5.1 Obstetric Complications At present, foetal hypoxia is the only OC that has been studied in relation to potential G × E interactions for brain structure and schizophrenia. van Erp et al. (2002) found hippocampal volume to be associated with genetic risk for schizophrenia; the higher the genetic risk, the smaller the hippocampal volume. Smaller hippocampal volumes were found in individuals with schizophrenia who experienced foetal hypoxia, although such an effect was not found in healthy relatives or controls (van Erp et al., 2002). Cannon et al. (2002a) analysed the same sample and found foetal hypoxia to be associated with lower grey matter (predominately in the temporal lobe) and higher cerebral spinal fluid in patients *and* their siblings but not in healthy controls. The latter results suggest clearer evidence of a G × E interaction and that cortical as opposed to subcortical parameters may be predominantly implicated in OC effects. Such interactions are yet to be investigated in relation to CT and SA.

1.5.2 Cannabis Use Recent studies have investigated whether the potential impact of cannabis on brain structure interacts with schizophrenia risk. Welch and colleagues, found cannabis to be associated with, and a predictor of, increased ventricular (Welch et al., 2011a) and thalamic (Welch et al., 2011b) volume in those at genetic risk for schizophrenia but not in healthy controls. No studies have yet investigated this relationship in CV. In relation to CT, Habets et al. (2011) found cannabis to be associated with CT reductions in schizophrenia patients compared to patients who do not use the drug. A similar pattern was evident in those at risk of developing schizophrenia (siblings) but not in healthy controls (Habets et al., 2011). Furthermore, French et al. (2016) found decreased CT to be associated with a higher PGRS-SCZ in males who used cannabis by the age of 16 compared to non-users, in three independent, population-based cohorts. The authors posit that cannabis use may disrupt cortical maturation and thus, early cannabis use may moderate the link between genetic liability for schizophrenia and these cortical abnormalities (French et al., 2015). No G × E studies were found for SA.

Whilst researchers have attempted to disentangle the relationship between genetic and environmental risk factors for schizophrenia and how they impact upon cortical structure, further work is still required (Geoffroy et al., 2013). For example, many cortical structures have not been considered nor have other environmental risk factors (adverse events, urbanicity and migration) that are consistently associated with an increased risk of schizophrenia (Murray et al., 2017, Stilo et al., 2011, Stilo and Murray, 2010, Dean and Murray, 2005).

1.6 Conclusion

Despite the detrimental impact of schizophrenia on neurodevelopment and the poor prognosis of the disorder, recent research suggests a more optimistic outlook whereby the disorder can be more stable and manageable (Zipursky et al., 2018). Early detection is considered important for better clinical outcome (Zipursky et al., 2018, Murray et al., 2017, Bois et al., 2015a, Agius et al., 2011, Lawrie et al., 2011, Häfner and Maurer, 2006, McGlashan and Johannessen, 1996) and, thanks to recent advances in research methodologies and sample collection, has become more achievable. Thus, the more schizophrenia-associated risk factors that we can identify, the easier it will be to construct a fuller clinical picture of the disorder and, in turn, make it easier to detect in its infancy.

This overview details evidence of cortical structure abnormalities associated with schizophrenia, in addition to several genetic and environmental risk factors for developing the disorder as well as G × E interactions. To illustrate, evidence is provided which suggests that schizophrenia-associated cortical structure deficits are associated with a genetic liability for the disorder, whilst other studies provide support for environmental risk factors altering neuroimaging markers. However, current literature is limited, and further investigation of the link between environmental risk factors individually and in accumulation are necessary. A better understanding of environmental risk factors for schizophrenia may enable clinicians to reduce symptom severity or prevent disorder onset. Furthermore, a better understanding of G × E interactions will enable researchers and clinicians to develop efficacious preventative strategies resultant from greater knowledge of schizophrenia development. A more

comprehensive view of the links between genetic, environmental and cortical imaging markers in schizophrenia aetiology or prognosis, will ultimately enable researchers to devise and execute successful interventions.

This thesis aims to investigate the potential effects of five environmental risk factors for schizophrenia, as well as a genetic risk factor (PGRS-SCZ), on three different cortical metrics (CV, CT and SA). A case-control (Chapter Two) sample will be used to first determine if a link exists between schizophrenia and genetic and/or environmental risk factors and a large population-based sample (Chapters Three and Four) will be employed to try to replicate such relationships. Additionally, the work contained within this thesis will attempt to separate potential genetic and environmental effects on cortical structure using a range of statistical methodologies.

Chapter Two

The relationship between environmental and polygenic risk for schizophrenia and cortical thickness in SFMH

2.1 Background

This chapter aims to determine if environmental risk factors (previously outlined in Chapter One) or a PolyGenic Risk Score for Schizophrenia (PGRS-SCZ) can impact upon cortical thickness. Reductions in this parameter, particularly in the frontal and temporal regions, are commonly associated with schizophrenia (Hedman et al., 2016, Crespo-Facorro et al., 2011, Hartberg et al., 2011, van Haren et al., 2011, Yang et al., 2010, Rimol et al., 2010, Goldman et al., 2009, Nesvåg et al., 2008, Kuperberg et al., 2003) however, what causes these deficits is unclear. According to neurodevelopmental theories of the disorder, environmental and genetic factors may initially disrupt cortical development, making individuals more susceptible to developing schizophrenia (Weinberger, 2017, Brown, 2011, Weinberger, 1987). As outlined in Chapter One, both the genetic and environmental components must be investigated in order to fully understand schizophrenia onset, development and prognosis (Stepniak et al., 2014, Stilo and Murray, 2010, Dean and Murray, 2005). Although there is a vast amount of research outlining the links between genetic susceptibility to schizophrenia and cortical structure, as well as epidemiological evidence for a number of environmental risk factors to be associated with higher incidence or greater risk for the disorder (Brown, 2011, Stilo and Murray, 2010, Mäki et al., 2005, Dean and Murray, 2005); it is less clear how environmental factors associate with cortical structure, and their relationship with said genetic liability.

In this chapter we introduce a method for determining whether an individual or accumulation of environmental risk factors, as well as the PGRS-SCZ can impact upon cortical thickness. Evidence of major risk factors being associated with this cortical structure could help us disentangle the relationship between schizophrenia risk, the disorder itself and cortical thickness deficits.

This chapter has been submitted and accepted as a journal article entitled '*Effects of environmental risk and polygenic loading for schizophrenia on cortical thickness'* at *Schizophrenia Research.* The following chapter has been adapted to match the format of the current thesis. I can also confirm that I was responsible for the design of the experiment, analysing the data and writing the paper for this submission.

2.2 Paper: Effects of environmental risks and polygenic loading for schizophrenia on cortical thickness

2.3 Abstract

Background: There are established differences in cortical thickness (CT) in schizophrenia (SCZ) and bipolar (BD) patients when compared to healthy controls (HC). However, it is unknown to what extent environmental or genetic risk factors impact on CT in these populations. We have investigated the effect of Environmental Risk Scores (ERS) and Polygenic Risk Scores for SCZ (PGRS-SCZ) on CT.

Methods: Structural MRI scans were acquired at 3T for patients with SCZ or BD (*n* = 57) and controls (*n* = 41). Cortical reconstructions were generated in FreeSurfer (v5.3). The ERS was created by determining exposure to cannabis use, childhood adverse events, migration, urbanicity and obstetric complications. The PGRS-SCZ were generated, for a subset of the sample (Patients = 43, HC = 32), based on the latest PGC GWAS findings. ANCOVAs were used to test the hypotheses that ERS and PGRS-SCZ relate to CT globally, and in frontal and temporal lobes.

Results: An increase in ERS was negatively associated with CT within temporal lobe for patients. A higher PGRS-SCZ was also related to global cortical thinning for patients. ERS effects remained significant when including PGRS-SCZ as a fixed effect. No relationship which survived FDR correction was found for ERS and PGRS-SCZ in controls.

Conclusions: Environmental risk for SCZ was related to localised cortical thinning in patients with SCZ and BD, while increased PGRS-SCZ was associated with global cortical thinning. Genetic and environmental risk factors for SCZ appear therefore to have differential effects.

This provides a mechanistic means by which different risk factors may contribute to the development of SCZ and BD.

2.4 Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) are psychiatric disorders characterised by overlapping symptomatology (Bois et al., 2015a, Hilty et al., 2006) and multifactorial aetiologies (Hilty et al., 2006, Jablensky, 1997). Both are highly heritable (around 80%) due to a large number of relatively common genes of small effect (Matheson et al., 2011, McGuffin et al., 2003). Both have been proposed to be consistent with a neurodevelopmental model (Rapoport et al., 2012, Weinberger, 1987) which posits that SCZ and related disorders are influenced by both genetic and environmental factors impacting on the brain, at different developmental stages (Rapoport et al., 2012). Significant widespread cortical thinning is consistently found when comparing SCZ and BD patients to healthy controls (HC) (Knöchel et al., 2016, Nesvåg et al., 2012, Rimol et al., 2010, Goldman et al., 2009, Kuperberg et al., 2003). It is unclear however whether these differences are related to genetic and/or environmental risk factors previously associated with SCZ. Elucidating these components would help to further understand the underlying aetiologies of these disorders.

Decreases in grey matter volumes have been found before disease onset (McIntosh et al., 2011) and thinner cortices have been noted in SCZ patients when compared to HC in all lobes (Rimol et al., 2010, Goldman et al., 2009, Kuperberg et al., 2003). However, the most consistent findings have suggested that cortical thinning is most prominent in frontal and temporal regions (Sprooten et al., 2013, van Haren et al., 2011, Rimol et al., 2010, Goldman et al., 2009, Kuperberg et al., 2003), where it continues to decline after disease onset (Cobia et al., 2012). Despite reports of disease specific cortical alterations associated with BD, for example, in orbitofrontal regions (Knöchel et al., 2016), many studies have also highlighted cortical thinning findings which overlap with the aforementioned SCZ deficits (Hanford et al., 2016, Knöchel et al., 2016, Rimol et al., 2010). Hence, frontal and temporal lobes are regions of interest for investigation of factors that could impact cortical deficits within SCZ and BD.

Both SCZ and BD have been associated with several environmental risk factors (Marangoni et al., 2016, Lawrie et al., 2011, van Os et al., 2010). Cannabis use, childhood adversity and obstetric complications (OC) have the strongest epidemiological evidence for an association with an increased risk of SCZ and BD, (Marangoni et al., 2016, Radhakrishnan et al., 2014, Stepniak et al., 2014, Matheson et al., 2013, Rapoport et al., 2012, van Os et al., 2010, Krabbendam & van Os, 2005). Urbanicity and migration are also strongly linked to SCZ (Stepniak et al., 2014, Rapoport et al., 2012, van Os et al., 2010, Krabbendam & van Os, 2005); however, as environmental risk factors for BD the evidence is less conclusive (Demjaha et al., 2012). Nevertheless, both migration and urbanicity have been linked to an increased incidence of BD (Cantor-Graae & Pedersen, 2013, Pedersen & Mortensen, 2006).

Although the evidence is limited, some of these factors have also been linked to deficits in cortical volume and thickness. Cannabis use has been associated with reduced global and frontal lobe volumes (Welch et al., 2011a), cortical thinning in general (Habets et al., 2011), and, more specifically, in dorso-lateral prefrontal cortex (DLPFC) and anterior cingulate cortex (Rais et al., 2010). Childhood adversity/trauma has been associated with cortical thinning globally (Habets et al., 2011) and in the limbic system (Souza-Queiroz et al., 2016), as well as decreased subcortical structure volumes (Barker et al., 2016b, Hoy et al., 2012). So far, OC have not been significantly related to cortical thinning (Haukvik et al., 2009; Smith et al., 2015) but birth complications have been previously linked to reduced hippocampal and cortical volume (Cannon et al., 2002a; van Erp et al., 2002) and may, alone or in accumulation with other risk factors, be linked to deficits in cortical thickness (CT). Migration and urbanicity are yet to be investigated in relation to CT but urbanicity has been linked with decreased grey matter volume in DLPFC within a healthy sample (Haddad et al., 2015).

Our knowledge of how these environmental risk factors impact upon CT in SCZ and BD is therefore inconclusive. Given a lack of knowledge about how these factors confer risk, it is desirable to determine if an accumulation of these risk factors has additional effects; some are

likely to occur and impact development at different stages of life (Dean & Murray, 2005; Stepniak et al., 2014) and several of these factors can be experienced by any individual. Prima facie, it seems likely that a higher number of insults may result in greater biological effects. One aim of the current study is therefore to determine the impact of environmental risk factors, in accumulation, on CT.

Genome Wide Association Studies (GWAS) have advanced our understanding of the genetic underpinnings of SCZ and BD. Recently, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (SWG-PGC, 2014) GWAS identified 108 genetic loci associated with SCZ, as well as several other markers that failed to reach genome-wide significance, suggesting a polygenic foundation to SCZ, with many genetic variants of individually small effect contributing to the overall phenotypic variation (International Schizophrenia Consortium., 2009). Strong evidence also exists for a polygenic basis for BD, with a strong overlap in the genetic variants associated with SCZ and BD (CDG-PGC, 2013, SPGWASC, 2011, Purcell et al., 2009). Using the summary data from the SWG-PGC GWAS (including alleles associated with the risk of SCZ as well as their effect sizes) as the training dataset, PGRS for SCZ (PGRS-SCZ) can be created in an independent sample. Risk variants in the independent sample which are common to the training dataset are identified, these are then weighted by the effect sizes reported in the SWG-PGC GWAS and summed across individual genotypes in the independent sample (Euesden et al., 2015, SWG-PGC, 2014, Purcell et al., 2009). Higher positive scores indicate a greater polygenic risk for disorder.

Several studies have investigated the effect of these PGRS-SCZ on clinical and cognitive phenotypes (Whalley et al., 2016, Stepniak et al., 2014, McIntosh et al., 2013). Thus far, structural neuroimaging phenotypes have been assessed with regard to the first SWG-PGC GWAS data, which identified 7 associated loci (SPGWASC, 2011), with inconsistent results (Papiol et al., 2014, Terwisscha van Scheltinga et al., 2013), making further investigation warranted.

Despite the fact that risk variants have been identified for BD separately (PGWASC-BDWG, 2011), there is still a substantial amount of shared variation between these psychiatric disorders (CDG-PGC, 2013, SPGWASC, 2011). Furthermore, PGRS-SCZ have been previously used for analysis within a combined BD and SCZ patient group (Ruderfer et al., 2014). Therefore, as the intention of the current study is to determine whether risks common to the development of both BD and SCZ are linked to CT, and the SCZ GWAS is more highly powered than the BD GWAS (SWG-PGC, 2014, PGWASC-BDWG, 2011), we have used the PGRS-SCZ. A second aim of the current study is to determine if a relationship exists between PGRS-SCZ, created using the most recent PGC SCZ data, and CT.

Within the current study, global, frontal and temporal regions of CT were analysed to determine their relationship with PGRS-SCZ and environmental risk associated with SCZ. We hypothesised that both PGRS-SCZ and an accumulation of environmental risk factors would be inversely associated with cortical thinning in these regions, for both the patients and controls separately and when assessing differences between patients and controls. Due to the aforementioned overlap between structural findings, environmental, and genetic risk factors, and in order to increase power within the sample, SCZ and BD patient data were combined into one patient groups for analyses.

2.5 Methods

2.5.1 Participants Detailed participant information has been reported previously (Whalley et al., 2015). Briefly, participants were recruited as part of the Scottish Family Mental Health Study (SFMH), approved by the Multicentre Research Ethics Committee for Scotland (09/MRE00/81). Detailed clinical and MRI data were obtained for HC (*n* = 41) and patients with a DSM-IV diagnosis of SCZ (*n* = 38) or BD (*n* = 20) aged between 18 and 67 years. Clinical diagnoses were established using the structural interview for the DSM-IV (SCID; (First et al., 2002) conducted by one of two trained psychiatrists. For analyses purposes, SCZ and BD participants were combined into one patient group. **Table 2.1** shows demographic information for both groups. Secondary tests, analysing associations between the SCZ and

BD groups separately, were also conducted and can be found, in full, in **Appendix A** (p14-20).

Table 2.1 Demographic and clinical characteristics for healthy controls (HC) and the combined patient group in the current study

	HC Mean (S.D)	**Patient** Mean (S.D)	**t/X²**	***P***
N	41	57		
Age	38.22 (14.39)	39.21 (11.80)	0.47	0.64
Gender (Male/Female)	23/18	37/20	0.45	0.50
Illness Duration in years	-	17.95 (11.81) Range: 0-45	-	-
Age of Onset in years	-	21.96 (9.17) Range: 7-53	-	-
CPZ Equivalent (ENIGMA)	-	252.55	-	-
PANSS Total	31.54 (4.21)	54.38 (18.30)	-9.02	$6.14\times^{-13***}$
PANSS Positive	7.17 (0.67)	12.45 (5.25)	-7.44	$5.57\times^{-10***}$
PANSS Negative	7.29 (1.42)	13.38 (6.92)	-6.40	$2.48\times^{-08***}$
PANSS General	17.07 (3.55)	28.55 (9.10)	-8.59	$8.22\times^{-13***}$
SES			29.71	$1.68\times^{-05***}$
Unemployed/Retired	1/5	26/8		
Manual/non-manual	8/28	7/15		
Young Mania Rating Scale	0.14 (0.82)	2.75 (3.72)	-4.96	$6.39\times^{-06***}$
Hamilton Depression Rating Scale	0.87 (3.04)	9.98 (8.07)	-7.50	$1.43\times^{-10***}$
Paternal Age	-	31.05 (6.68)	-	-
NART IQ	111.2 (6.89)	110.5 (9,62)	0.44	0.66
PGRS-SCZ	-0.33	0.25	-2.62	0.01^{*}
ERS for 3 factors	1.29 (0.87)	1.68 (0.76)	-2.31	0.02^{*}
ERS for 5 factors	-	2.51 (1.09)		

$^{***}p_{corr} \leq .001$, $^{**}p_{corr} \leq .01$, $^{*}p_{corr} \leq .05$, $^{\cdot}\ p_{corr} \leq .10$, **HC** = Healthy controls, **S.D** = Standard deviations, **PANSS** = Positive and negative syndrome scale, **SES** = Socioeconomic status, **CPZ** = Chlopromazine, **ENIGMA** = Enhanced neuroimaging genetics through meta-analysis (http://www.enigma.ini.usc.edu), **NART IQ** = National adult reading test intelligence quotient (measure of premorbid intelligence), **PGRS-SCZ** = Polygenic risk score for schizophrenia, **ERS** = Environmental risk score

2.5.2 Imaging Procedures Magnetic Resonance imaging was performed at Edinburgh's Clinical Research Imaging Centre (CRIC) (http://www.cric.ed.ac.uk/) on a Siemens Verio 3T MRI system (Siemens Medical Systems, Erlangen). Structural brain images were acquired using a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE)(repetition time 2300ms, echo time 2.98ms, inversion time 900ms, flip angle = 9°)

with an isotropic voxel resolution of 1mm parallel to AC-PC plane, field of view = 256mm × 256mm.

Brain scans were anonymised at the time of acquisition and a set protocol was adhered to for pre-processing of scans, regardless of clinical status. Structural images were processed using FreeSurfer (v5.3) (http://surfer.nmr.mgh.harvard.edu/fswiki/) to quantify thickness of cortical anatomical regions, volumetric segmentation, cortical surface reconstructions and cortical parcellation. See **Appendix A2.1.1** (p1) for full procedure. The Desikan-Killiany atlas was used to define cortical anatomical regions (Desikan et al., 2006). A list of the regions of interest included in frontal and temporal lobes, using this atlas, can be found in **Appendix A2.1.1** (p1)**.**

A trained rater (E.N) checked all scans for inaccuracies, blinded to group status. All scans were edited adhering to FreeSurfer procedures (http://freesurfer.net/fswiki/Edits) in order to increase the accuracy of the pial surface. Following this procedure, one scan was removed due to defective surface generation that could not be corrected by manual editing (HC=41, Patient=57). Average global and lobar CT values were extracted from each scan for analysis.

2.5.3 Environmental Measures Environmental risk information was collected for all 98 participants. The risk factor measures and subsequent calculation of an Environmental Risk Score (ERS) were based upon methods developed by Stepniak et al. (2014) and included three factors for controls; Childhood Adverse Events (CAE), Migration, and Cannabis Use, with a further two for the patient group; OC and Urbanicity. Environmental measures were defined as follows: *CAE* – measured using the Childhood Life Events Questionnaire (CLEQ, www.bdrn.org) which determined if participants had experienced one or more event out of a possible list of 13 adverse childhood events including death of a parent/friend, parental divorce and personal/parental hospitalisation. Abuse and bullying are not specifically enquired about however, a final question allows participants to disclose any other CAE not previously specified. Risk was recorded if the participant experienced one or more of the possible events as opposed to none; *Migration* – whether the participant migrated to the United Kingdom from

another country; *Cannabis Use* – any recorded cannabis use before the time of scan; *OCs* – any deviation from normal pregnancy or delivery (e.g. premature birth, jaundice); *Urbanicity* – calculated using the measure from Stepniak et al. (2014), to determine the cities that patients lived in from birth to 18 years old. Each city was placed into a category depending on its population (1: </= 10,000, 2: 10,001-50,000, 3: 50,001-100,000, 4: > 100,000) and was multiplied depending on the number of years spent living in that place. This was repeated for each city if the participant relocated and all scores were summed. The total score was then split into one of 2 groups - rural (score 18-45) and urban (score 46-72) upbringing, with placement in the urban group conferring risk. Environmental measures were scored as 1 or 0; with 1 representing that the risk was present for each participant. Frequencies of the individual factors for the combined patient groups and controls are displayed in **Appendix A2.1.3** (p2-3). Participants with unavailable information (NA) on factors were rated, conservatively, as 0, however, analyses with NA removed were also conducted with results reported in **Appendix A2.2.3** (p6-9). The continuous ERS was determined by totalling the number of environmental measures experienced by each participant.

2.5.4 Genotyping and Derivation of PGRS-SCZ Information on the genotyping process are presented in **Appendix A2.1.2** (p2)**.**

Polygenic profile scores were generated using imputed genotype data. Imputation was performed in accordance with the ENIGMA 1000 genomes protocol (ENIGMA2 Genetics Support Team, 2013) Single nucleotide polymorphisms (SNPs) with an imputation R-squared quality score of > 0.3 were retained for further analysis resulting in 6,145,246 SNPs. All subsequent analyses were performed in PLINK (Purcell et al., 2007). Further QC criteria were applied to imputed data. Individuals with missingness > 2% were excluded, as were SNPs with a genotype call rate of < 98%, Hardy-Weinberg equilibrium p-value < 1×10^{-6}, a minor allele frequency of < 5%, or those that were strand ambiguous. Clump-based linkage disequilibrium pruning (r^2 0.2, 300kb window) was performed to create a SNP-set in approximate linkage equilibrium. Marker weights (logarithm of the Odds Ratio) and p-value association statistics for SNPs were derived from the most recent PGC GWAS of schizophrenia (9.8 million

autosomal SNPs) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Five scores were generated for each individual, using SNPs selected according to the significance of their association with the phenotype in the discovery GWAS at nominal *P*-value thresholds of ≤ 0.01, 0.05, 0.1, 05, 1, as previously described (International Schizophrenia Consortium, 2009). These data were not available for 11 of the patients and 8 of the controls and they were therefore excluded (Patients = 46, HC = 33).

Multi-dimensional scaling (MDS) was conducted to identify outliers within the population stratification using previously described protocols (ENIGMA2 Genetics Support Team, 2013). In plotting the MDS components, three outliers were identified and removed (**Appendix A, Fig A2.1,** p3). Four MDS components were included in subsequent PGRS-SCZ analysis models within this study, consistent with previous publications (Whalley et al., 2015, McIntosh et al., 2013). Where sibling pairs were present in the sample, one half was removed to avoid relatedness issues, making the final sample with genotyped information HC = 32, Patients = 43.

2.5.5 Statistical Analysis Statistical analyses were conducted in R (v3.2.2). The effects of left and right global, frontal and temporal CT were investigated in line with our hypotheses. SCZ and BD patient data were combined into one patient group due to overlap between genetic risk, environmental risk and structural MRI findings. However, a secondary analysis examining the patients separately was performed. Some of these results are reported below, with full results reported in **Appendix A** (p14 - 20).

Firstly, we assessed whether an accumulative ERS and, post-hoc, individual environmental risks were related to CT. Secondly, we tested for associations between CT and PGRS-SCZ and finally, we calculated whether any environmental effects remained after controlling for potential genetic effects. As the aim of the study was to determine whether there was an effect of environmental and polygenic risk on CT, and more environmental information was available

for patients than controls, analyses were conducted separately for each of these groups. However, we also tested for potential differential effects when comparing patients and controls using the three environmental factors common to both groups, as well as the PGRS-SCZ. ANCOVAs were run for each anatomical structure with the structure of interest entered as the outcome variable and ERS/PGRS-SCZ as the predictor variable. Results for all lobar structure analyses for ERS and PGRS-SCZ analyses were corrected for multiple comparisons using a False Discovery Rate (FDR) correction, with a rate of p=0.05 (Genovese et al., 2002). The same procedure was also followed for analysis of the SCZ and BD groups separately. Post-hoc analyses were run to test for the effects of individual environmental risk factors on CT. Due to these factors all being correlated with the ERS (**Appendix A2.2.1,** p4), post-hoc analyses were FDR corrected across lobes and all individual environmental risk factors.

For the ERS analyses, using the combined patient group (as well as the SCZ and BD groups separately) and controls separately, covariates included age (mean centred) and gender, with group (SCZ/BD) added as a fixed effect within patient models to control for potential group differences. ERS was the predictor of interest within the main environmental analysis. For additional post-hoc analyses the individual risk factor was the predictor variable. Age (mean centred), gender, and group for the patient analyses, were also included as fixed effects in the PGRS-SCZ analyses as well as four MDS components and the standardised PGRS-SCZ at threshold $P \leq 0.1$. This threshold was utilised as it was shown to explain the most phenotypic variance in the discovery cohort (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Results at the 4 other thresholds ($P \leq 0.01$, 0.05, 0.5 and 1) are presented in **Appendix A2.2.4** (p10-13). Total average thickness was added as a covariate for all frontal and temporal lobar analyses. The same models with the inclusion of an ERS or individual environmental risk factor/PGRS-SCZ by group interaction factor was also run to investigate potential group differences between the combined patient group and controls as well as between the SCZ and BD groups separately.

A further analysis model, including the above ERS covariates, the PGRS-SCZ variables included as fixed effects and ERS as the predictor variable, was tested to determine the effect of ERS whilst controlling for PGRS-SCZ.

Power was also calculated for the environmental risk analyses. As there is no previous effect size in the literature that links an accumulative ERS to CT, we estimated this based on a review by Lawrie et al. (2011), which includes the OR of many of the risk factors within the current study. Based on this review, we took an overall summary OR of 2 which is conservative as the OR for immigration for example is 5 (Lawrie et al., 2011). We converted this OR to an effect size using methods described in Chinn et al. (2000). Using this effect size in conjunction with sample size information for the current sample, we calculated power for the current study using the 'pwr' package in R. The results suggest that we have 88-96% power to detect relationships at $p = 0.05$ within the current sample.

Chlorpromazine equivalents (CPZE) of patient's antipsychotic use were calculated using previous methods (Woods, 2003). Spearman's rank correlations revealed no significant relationship between CPZE and the current brain parameters.

2.6 Results

2.6.1 Group Differences No significant differences were found for age, gender or premorbid IQ (NART; National Adult Reading Test) between the combined patient group and controls, but significant differences were found for Socioeconomic status, Young Mania Rating Scale, Hamilton Depression Rating Scale and symptom severity (**Table 2.1**).

There was a significant difference in CT between patients and controls globally (left and right hemispheres), and in right temporal lobes (**Table 2.2**); patients had significantly thinner global (left and right) and right temporal cortices compared to controls.

Table 2.2 Mean group differences in cortical thickness for healthy controls (HC) and patients with associated standard deviations (S.D) and *p* values

	HC (*n* = 41)	**Patients** (*n* = 57)		
	Mean (S.D)	**Mean (S.D)**	**F**	***P***
Left	2.52 (0.10)	2.44 (0.11)	11.63	$1.00\times^{-03***}$
Right	2.51 (0.09)	2.43 (0.10)	14.78	$2.00\times^{-04***}$
Frontal Left	2.56 (0.11)	2.49 (0.13)	0.83	0.36
Frontal Right	2.49 (0.11)	2.44 (0.13)	3.64	0.06**.**
Temporal Left	2.86 (0.12)	2.74 (0.17)	1.61	0.21
Temporal Right	2.91 (0.12)	2.77 (0.15)	5.60	0.02^{*}

$^{***}p_{corr} \leq .001$, $^{**}p_{corr} \leq .01$, $^{*}p_{corr} \leq .05$, **.** $p_{corr} \leq .10$, **S.D** = Standard deviation

A significant difference in PGRS-SCZ was also evident between groups (**Table 2.1**); patients had a higher mean score than controls at the $P \leq 0.1$ threshold ($t_{69.17} = -2.62$, $p = 0.01$). **Appendix A2.2.4** (p10-13) presents differences at other thresholds.

There was also a significant group difference in ERS (**Table 2.1**); patients experienced a higher mean number of environmental risks compared to controls ($t_{78.75} = -2.3$, $p = 0.02$).

Analyses were also conducted to determine potential group differences between SCZ and BD with some results reported below and in **Appendix A** (p14-20). No significant differences were found between these groups, with the exception of PANSS Positive Symptoms.

2.6.2 Patient Analysis

2.6.2.1 ERS Analysis A significant main effect was found for ERS ($F_{1,51} = 7.23$, $p = 0.01$) which survived FDR correction ($p_{corr} = 0.04$); an increase in ERS was associated with a thinner right temporal cortex (**Table 2.3**).

Table 2.3 Adjusted Mean Thickness in Right Temporal Lobe dependent on the number of environmental risk factors experienced by the patients (*n* = 57)

	0 Risks	**1 Risk**	**2 Risks**	**3 Risks**	**4 Risks**	**5 Risks**
Adjusted Mean Thickness (mm)	2.85	2.82	2.79	2.76	2.73	2.70
S.E	0.03	0.02	0.01	0.01	0.02	0.03

S.E = Standard error

2.6.2.1.1 Secondary Patient Analysis – ERS in SCZ and BD Groups Separately For the SCZ patients, there was a significant effect of ERS where an increase in environmental risk scores was related to lower cortical thickness in the right temporal lobe ($F_{1,32}$=6.57, p=0.02). This effect was not significant within the BD patients but the same pattern was present (**see Tables 2.4 and 2.5** and **Appendix A2.2.4** (p10-14).

Table 2.4 Adjusted Mean Thickness in Right Temporal Lobe dependent on the number of environmental risk factors experienced by Schizophrenia patients (*n* = 37)

	0 Risks	1 Risk	2 Risks	3 Risks	4 Risks	5 Risks
Adjusted Mean Thickness (mm)	2.85	2.82	2.79	2.75	2.72	2.68
S.E	0.037	0.026	0.017	0.017	0.025	0.036

S.E = Standard error

Table 2.5 Adjusted Mean Thickness in Right Temporal Lobe dependent on the number of environmental risk factors experienced by the Bipolar Disorder patients (*n* = 20)

	0 Risks	1 Risk	2 Risks	3 Risks	4 Risks	5 Risks
Adjusted Mean Thickness (mm)	-	2.82	2.81	2.79	2.77	-
S.E	-	0.026	0.013	0.014	0.027	-

S.E = Standard error

2.6.2.2 Post-hoc Analysis of Individual Environmental Risk Factors Post-hoc analyses of individual environmental risk factors revealed no significant main effects which survived FDR correction, for the combined patient group (**Appendix A2.2.3.1,** p5-6). No effects of group (SCZ, BD) were found for the ERS or individual environmental risk analyses.

2.6.2.3 PGRS-SCZ Analysis A significant main effect of PGRS-SCZ on Global CT was found in left ($F_{1,33}$ = 4.33, p = 0.05) and right ($F_{1,33}$=4.54, p = 0.04) hemispheres, due to a negative relationship between PGRS-SCZ and CT (**Fig. 2.1a and b**). No main effect of group

was found in these regions. No significant effects were found for any other structures (**Appendix A2.2.4.1,** p10).

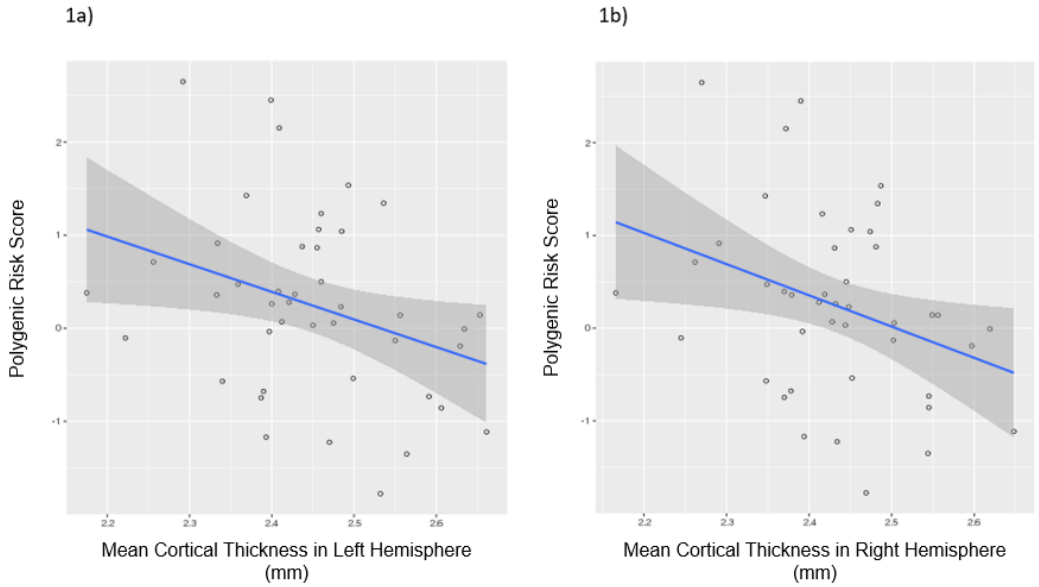

Fig. 2.1 Scatter plots showing global a) left and b) right cortical thickness, in mm^2, and polygenic risk scores for schizophrenia in the combined patient group (SCZ = 37, BD = 20)

2.6.2.3.1 Secondary Patient Analysis – PGRS-SCZ in SCZ and BD Groups Separately For both SCZ and BD patients, the pattern of results suggests that as polygenic risk scores increase, global and left temporal lobe cortical thickness values decrease (**See Fig A2.3 and A2.4, Appendix A2.2.4** (p10-13). This was not a significant effect within the BD patients and only reached trend level for SCZ patients in the left ($F_{1,15}$=3.51, p=0.08) and right ($F_{1,15}$=3.63, p=0.08) hemisphere.

2.6.2.4 ERS controlling for PGRS-SCZ Analysis When adjusting for possible effects of PGRS-SCZ, the main effects of ERS on CT in right temporal lobe, for the combined patient group, remained significant ($F_{1,31}$ = 5.74, p = 0.02).

2.6.2.4.1 Secondary Patient Analysis – ERS controlling for PGRS-SCZ in SCZ and BD Groups Separately The effect of higher ERS relating to lower right

temporal CT in the SCZ patients remained significant when controlling for potential effects of PGRS-SCZ ($F_{1,13}$=6.46, p=0.03) (see Appendix A, p10-13).

2.6.3 HC Analyses

2.6.3.1 ERS Analysis A main effect of ERS was apparent in controls within left and right temporal lobes but did not survive FDR correction. The pattern of this effect suggested that a higher ERS was associated with thicker temporal cortices.

2.6.3.2 Post-hoc Analysis of Individual Environmental Risk Factors Post-hoc analyses of individual factors suggested a main effect of CAE on left and right temporal lobes which did not survive FDR correction but displayed the pattern that those who had experienced CAE had greater CT within these regions, compared to those who had not. No other factor had a significant effect (**Appendix A2.2.3.2**, p7**)**.

2.6.3.3 PGRS-SCZ Analysis PGRS-SCZ did not have an effect on any of the structural parameters in controls. (**Appendix 2.2.4.2**, p11)

2.6.4 Interaction Analysis

2.6.4.1 Group × ERS Analysis There was a significant ERS by group interaction in right temporal lobes ($F_{1,91}$ = 6.23, p = 0.01); a higher risk score was associated with a thicker right temporal cortex within controls, but a thinner cortex within the combined patient group. However, after FDR correction, this result only revealed a trend towards significance (p_{corr} = 0.06). There were no other associations for any other structures and there were no significant main effects for ERS (**Appendix A2.2.3.3**, p8).

2.6.4.2 Post-hoc Analysis of Individual Environmental Risk Factors Post-hoc analyses revealed significant CAE by group interactions in right temporal lobe, surviving FDR

correction ($F_{1,91} = 6.27$, $p = 0.01$, $p_{corr} = 0.04$). This was due to thicker cortices for those controls who had experienced CAE compared to those who had not; whereas, in the combined patient group, the opposite pattern was apparent. No other individual risk factors were significant (**Appendix A2.2.3.3**, p8).

2.6.4.3 Group × PGRS-SCZ Analysis There was a significant main effect of PGRS-SCZ in left ($F_{1,64} = 8.41$, $p = 0.01$) and right ($F_{1,64} = 10.22$, $p < 0.01$) hemispheres; an increase in PGRS-SCZ was associated with a thinner cortex within these regions, regardless of group (HC versus combined patient group) (**Fig. 2.2a and b**). There were no other significant main effects (**Appendix A2.2.4.3,** p.12-13).

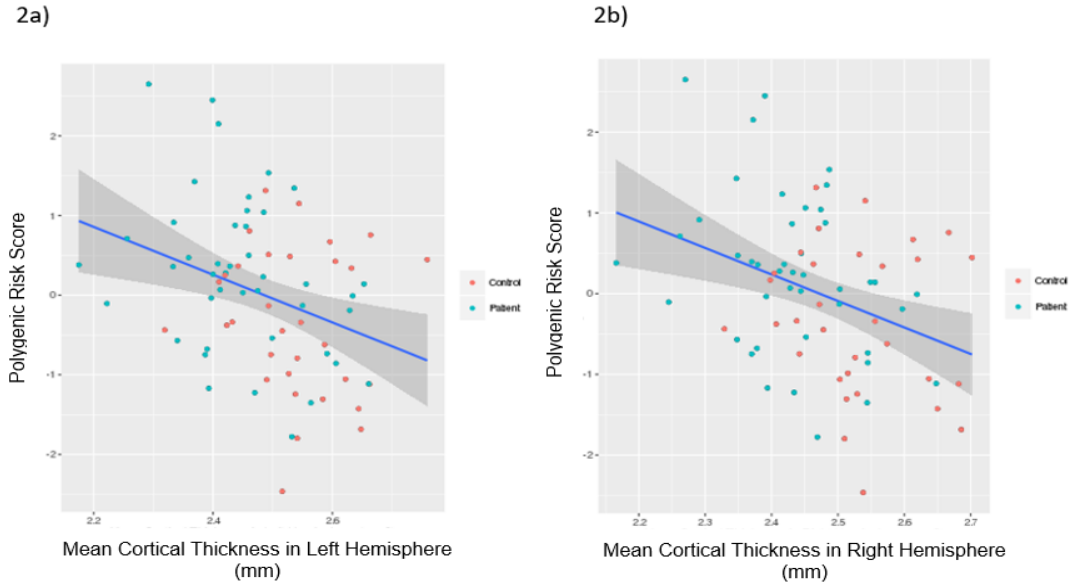

Fig. 2.2 Scatter plots showing that global a) left and b) right cortical thickness, in mm², is negatively associated with increased polygenic risk scores for schizophrenia, regardless of group (HC = 32, Patient = 43)

There was also a significant group by PGRS-SCZ interaction in left temporal lobe which withstood FDR correction ($F_{1,63} = 6.88$, $p = 0.01$, $p_{corr} = 0.04$). This was due to an increase in PGRS-SCZ being associated with a thinner cortex within patients (combined patient group) (**Fig. 2.3a**) but having no relationship in controls (**Fig. 2.3b**). No other interactions reached significance (**Appendix A2.2.4.3,** p.12-13).

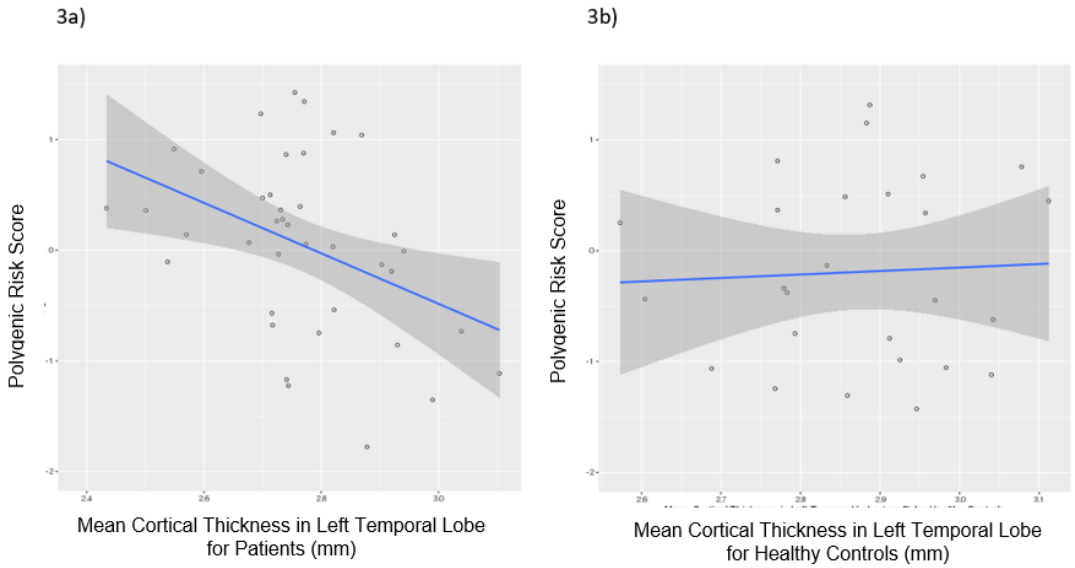

Fig. 2.3 Scatter plots showing left temporal lobe cortical thickness, is a) negatively associated with polygenic risk scores in the combined patient group (*n* = 43) and b) has no relationship with polygenic risk scores for schizophrenia in the HC group (*n* = 32)

2.6.4.4 Group × ERS controlling for PGRS-SCZ Analysis When controlling for potential effects of PGRS-SCZ on ERS, the significant ERS by group interaction remained for right temporal lobe ($F_{1,62} = 4.51$, $p = 0.04$). The CAE group interaction, also remained significant ($F_{1,62} = 7.22$, $p = 0.01$).

2.6.4.4.1 Secondary Patient Analysis - Group Interactions for SCZ and BD Groups Separately There were no significant interactions between ERS or PGRS-SCZ and group (SCZ versus BD patients) (see **Appendix A2.2.4**, p10-13).

2.7 Discussion

We examined whether an ERS, as well as PGRS-SCZ were associated with CT within a patient group (SCZ/BD) and HC. We report that an ERS for SCZ negatively affected right temporal CT within patients. Importantly, these effects were robust to controlling for PGRS-SCZ, and to FDR correction. Environmental risk factors were associated with a thicker cortex

within controls but did not survive FDR correction. Interaction analyses revealed a significant group by ERS interaction in right temporal lobe, in that, a thinner cortex was associated with increased ERS within patients whereas the opposite pattern was apparent within controls; albeit this interaction was a trend after FDR correction. There was also a significant group by PGRS-SCZ interaction in left temporal lobe, with higher PGRS-SCZ being related to a thinner cortex within patients whereas no relationship was apparent for controls.

Cortical thinning in temporal lobe is commonly found in patients with SCZ and BD (Hanford et al., 2016, van Haren et al., 2011, Rimol et al., 2010, Goldman et al., 2009, Kuperberg et al., 2003). As far as we are aware, our results provide the first evidence that an accumulation of environmental risk factors contribute to cortical thinning within this area. The opposite pattern (a higher ERS was associated with thicker temporal cortices) was seen in the separate analyses of control individuals, and in the interaction between the two groups, but these results did not survive FDR correction, possibly due to comparatively low power for these analyses.

Analysis of SCZ and BD groups separately also showed a higher ERS was associated with lower temporal CT however, this effect was not significant for the BD group. Notably, there were no individuals who had experienced zero or five environmental risk factors in the BD group thus, lack of an effect could reflect differences in susceptibilities to or likelihoods of experiencing such factors. For example, urbanicity has been less conclusively associated with an increased risk of BD compared to SCZ (Demjaha et al., 2012) but, BD risk factors have been less researched than that of SCZ (Rowland & Marwaha, 2018). Thus, the authors suggest that these differences are more likely due to reductions in power as a result of splitting the sample (Combined patient group = 57; SCZ = 37, BD = 20). Additionally, there were no significant group (SCZ versus BD patients) by ERS interactions, further suggesting that the overall pattern of effects was similar for both SCZ and BD patient groups.

We found a group (combined patient versus HC) by ERS interaction within right temporal lobe. Controls presented with a thicker right temporal cortex in association with experiencing CAE,

whereas patients who experienced the same insult had thinner temporal cortices. Although CAE have been formerly linked to thinner cortices in patients (Habets et al., 2011), they have not been previously associated with a thicker cortex in controls. Habets et al. (2011) found a thicker cortex to be associated with increased levels of developmental trauma in siblings of SCZ patients, but not in controls. We, however, did not previously find this effect in those at familial high-risk (Barker et al., 2016a). Our current replication of Habets et al. (2011) does support the possibility that experiencing CAE could thicken the cortex and may be related to resilience to developing a psychotic disorder. Within healthy populations, studies have shown that increased participation in practices which may promote mental wellbeing, such as meditation (Kang et al., 2013, Lazar et al., 2005) and physical exercise (Reiter et al., 2015), is associated with having a thicker temporal cortex, amongst other areas.

An important point to acknowledge is that we received less full histories for ERS derivation in controls than patients; however, the present study has also directly compared the environmental risk factors common to both patients and controls. We report a group by ERS interaction in right temporal CT, whereby higher ERS was associated with a thinner cortex within patients but a thicker cortex in controls. We also report a group by CAE interaction in right temporal lobe. These results suggest a differential effect of environmental risk in patients and controls but must be interpreted with caution and require replication in much larger cohorts.

We also report significant negative relationships between PGRS-SCZ and global CT within both the patient only analysis, and the full sample, irrespective of group. To our knowledge, this has not been previously reported – although we and others have reported thinner cortices in those at familial high-risk of SCZ (Sprooten et al., 2013, Byun et al., 2012, Goghari et al., 2007). Previously, increased PGRS-SCZ have been linked to a reduction in white matter volume (Terwisscha van Scheltinga et al., 2013) and decreased gyrification in general populations (Liu et al., 2016) however this is the first evidence linking genetic loading for SCZ

to CT. Based on our findings we hypothesise that genetic risk for SCZ could disrupt global CT during development and thereby increase the risk of developing SCZ.

Analysis of the SCZ and BD patient groups separately demonstrated the same pattern of a higher PGRS-SCZ being related to lower global CT however, this was not significant in the BD group and only reached trend level significance for the SCZ group. As, the sample size is reduced when investigating the effects of each group individually, we interpret this lack of significance as due to a lack of power and not a group difference however, future studies may benefit from addressing this more directly.

A significant group by PGRS-SCZ interaction was reported; a thinner cortex in left temporal lobe was associated with higher PGRS-SCZ in the combined patient group but had no association with PGRS-SCZ in controls. This suggests potential localised differential effects between patients and controls.

Analysis of the SCZ and BD patient groups separately showed no significant interactions between PGRS-SCZ and group, again, suggesting that the overall pattern of results was similar for both SCZ and BD patients.

In the current study, we used PGRS for SCZ rather than BD for several reasons. Firstly, we were interested in determining the commonalities between these disorders and how they may impact upon CT. Secondly, PGRS-SCZ have been used previously within BD populations (Ruderfer et al., 2014). Thirdly, the original GWAS for SCZ was better powered than that for BD (SWG-PGC, 2014, PGWASC-BDWG, 2011). However, it would be of interest for future studies to determine the effects of the PGRS for BD in a larger sample.

Given the potential interactive effects of genetic and environmental risk factors for SCZ on neuroanatomy, we conducted further analyses to determine whether the effects of environmental factors persisted after controlling for PGRS-SCZ. We report that all

environmental effects remained significant after so doing. We cannot rule out a gene-environment interaction of PGRS-SCZ and ERS on CT, but our results do suggest that the effects of genetic and environmental risks for SCZ are not the same.

A further limitation within this study is that we were not able to conduct corroborative interviews with parents, for example, therefore, it is likely that there is some missing information for individual environmental risk factors. We therefore decided that missing information (NAs) should be recorded as a 0 when calculating the ERS. This was considered the best approach, in order to include as much information as possible without potentially overstating the effect of environmental factors on brain structure. Additional analyses were also conducted with all NAs removed and are reported in **Appendix A2.2.3** (p5-9). The results of these analyses showed a similar pattern to those reported here but did not survive FDR correction. However, by removing the NAs a substantial amount of data was lost suggesting that the lack of significance may reflect low power rather than the lack of an effect. This outcome provides further support for the current approach, but analyses within a larger cohort is necessary to determine if the effects can be replicated.

Together, our results suggest that experiencing environmental risks for SCZ contributes to localised cortical thinning in patients with SCZ and BD. Higher genetic loading is associated with global cortical thinning but does not account for the effects of environmental risk. We thus provide further evidence for a neurodevelopmental model for SCZ which posits that both environmental and genetic factors contribute to the development of the disorders. Further, our results suggest that it might be possible to develop intervention strategies to address environmental risks for SCZ and measure their effect on CT.

2.8 Chapter Conclusion

Chapter Two suggests that environmental and genetic risk factors for schizophrenia can impact upon cortical thickness; with polygenic risk impacting the global structure and environmental factors being associated with more localised effects. Experience of an

accumulation of environmental risk factors were found to be related to lower cortical thickness in the temporal region. Thus, experiencing more than one environmental risk factor may be more detrimental to neurodevelopment, particularly if experienced early in the developmental process. However, to fully understand this relationship and how we can use this information to implement preventative measures, it is still of import that we investigate the specific effects of these individual factors on cortical structure. The next chapter will begin to address this issue using the factor birth weight as a proxy for obstetric complications.

In this chapter we also presented the first results of an association between higher PGRS-SCZ and lower global cortical thickness. However, given the lack of reproducibility of associations with total brain volume and PGRS-SCZ (Terwisscha van Scheltinga et al., 2013, Papiol et al., 2014, van der Auwera et al., 2015), this result requires replication (see Chapter Four). Moreover, due to the movement towards 'Big Data' (previously defined as > 1,000 scans; Smith and Nichols, 2018) in the imaging field, this sample size of 43 patients and 32 controls, may now be considered as inadequate to fully answer the question of the relationship between cortical thickness with schizophrenia-associated risk factors (Smith and Nichols, 2018), particularly in relation to genetics (He et al., 2017). The remainder of the thesis is therefore focused on further investigating the link between genetic and environmental risk factors for schizophrenia in relation to cortical structure in a much larger sample; UK Biobank (UKB).

Chapter Three

Exploring the causal relationship of birth weight on adult cortical brain structure in UK Biobank

3.1 Background

In Chapter Two it was suggested that environmental factors were related to cortical thickness but differently to PGRS-SCZ and at a more localised level. However, Chapter Two utilised data from the SFMH study which, despite being larger than most neuroimaging samples (Smith and Nichols, 2018) and containing some rich environmental risk factors and symptom severity phenotype data, is impeded by its sample size in relation to 'Big Data' standards (Smith and Nichols, 2018). The remaining chapters of the thesis therefore implement data from UKB.

UKB (http://www.ukbiobank.ac.uk/) is a large-scale population-based study that, on its completion aims to have 500,000 MRI brain scans at its disposal. The current release of data, which is the data that will be utilised for the majority of the current thesis, consists of 3,875 MRI scans which have measures of global, lobar and parcellated regions of the cortex. Furthermore, genetic data for 488,377 individuals is available in this sample.

Very recently, a further ~10,000 MRI scans were released however, as quality checks of this data had not been completed before submission of this manuscript, only the global measures of cortical volume, thickness and surface area from the first data release (excluding global cortical outliers) were used in the proceeding chapters. With regards to the SFMH sample, phenotypic information was recorded for five environmental factors thus, an accumulation effect could be tested. We searched the UKB database for variables that may match those used in the second chapter. Unfortunately, there was no cannabis information and the variables for adverse life events, urbanicity and migration were either not appropriate, not available within the current sample or, not ready for use at the time the current analyses were

conducted. No all-encompassing variable existed for obstetric complications however, birth weight, which has been previously used to infer intrauterine growth restriction (IUGR; Raznahan et al., 2012) was used as a meaningful proxy for this variable. We therefore only tested for an association between cortical structure and birth weight in the current chapter. As noted earlier, it is also important that we fully understand individual factors in relation to cortical structure, particularly if they are potentially modifiable (Johnson et al., 2017, Stilo and Murray, 2010). Obstetric complications are relatively common in the British population (occurring in around 6.9% of the population) (Johnson et al., 2017) and potentially modifiable through prenatal health initiatives (Clifford et al., 2013) thus, further investigation of its link to schizophrenia could prove fruitful and is thus studied in the upcoming chapter. As UKB is a population-based sample it will allow us to test if there is an effect of birth weight on brain structure in normal weight variations and therefore be more generalisable to non-clinical samples. In this chapter we also aim to determine if there are any causal links between these two phenotypes using the statistical analysis - Mendelian Randomisation. Additionally, we discuss what this potentially causal link could mean for brain development in general and in relation to the cortical deficits associated with schizophrenia.

This chapter is presented as the manuscript which has been submitted to the *International Journal of Epidemiology* in which, I am the first author. I can also confirm that I was responsible for the design of the experiment, analysing the data and writing the paper for this submission.

3.2 Paper: Exploring the causal relationship of birth weight on adult cortical brain structure in UK Biobank through Mendelian Randomisation

3.3 Abstract

Background: Differences in the brain's cortical organisation are linked to common psychiatric disorders and differences in cognitive ability. Low birth weight (BW, < 2.5kg) is associated with alterations in cortical brain structure, lower cognitive ability and psychiatric problems; suggesting that somatic foetal growth may be an important determinant of brain structure and

function in later life. However, the relationship between BW within the normal range and adult brain structure in the general population is little understood, including whether a causal relationship exists. We therefore sought to test if there is a causal relationship between BW and brain cortical morphology in an adult population-based sample using Mendelian Randomisation (MR).

Methods: The current sample included 1,680 individuals from the first release of brain imaging data from UK Biobank (UKB). Linear mixed effects models were first used to test for associations between BW and global and localised regions of brain cortical volume, surface area and thickness. Secondly, to test for causal relationships between BW and cortical metric phenotypes we used a two-sample MR framework, applying the inverse-variance weighted method.

Results: In the full population-based sample, higher BW was significantly associated with greater global cortical volume (β = .104, p = 2.86×$^{-07}$) and surface area (β = .100, p = 3.58×10^{-07}) but not thickness (β = -.054, p = .097). The strength of these effects were widespread across the cortical mantle, including frontal, temporal and insular regions (β range = .037, .069, p_{corr} range = .037, .010) as well as testing within the normal BW range (global cortical volume: β = .097, p = 5.64×10^{-06}; global surface area: β = .088, p =2.60×10^{-06}). We performed a GWAS of BW in UKB (n = 201,586) to identify BW-associated SNPs as proxies for BW. MR indicated significant causal links between lower BW and lower cortical volume of the insular lobe (β = .346, p_{corr} = .009), as well as surface area globally (β = .281, p = .009), in the insular lobe (β = .371, p_{corr} = .005) and middle temporal (β = .287, p = .045), medial orbitofrontal (β =.417, p_{corr} = .006) and IFG (β =.512, p_{corr} = .009) parcels.

Conclusions: Our findings extend previous studies providing evidence of a potential causal effect of BW, as indexed by genetic variants, on several measures of cortical volume and surface area. The current MR results may therefore also partially explain the links between increased risk of psychiatric and cognitive impairment in individuals with lower BW, even within the normal range.

3.4 Introduction

Cortical configuration is fully established during foetal life, and is followed by increases in thickness and surface area over the first two postnatal years (Lyall et al., 2015). Studies, using a range of imaging techniques, have identified cortical deficits both specific to and shared among common psychiatric disorders and their development (Birur et al., 2017, Norman et al., 2016, Savitz et al., 2013) as well as a decline in cognitive abilities (Cox et al., 2017). Early complications of pregnancy (such as preterm birth or intrauterine growth restriction; IUGR), which result in low BW, are closely associated with abnormal cortical structure (Kapellou et al., 2006, S. Miller et al., 2016). However, the effect of normal population variation in BW on adult cortical morphology is less well known. Since abnormalities of adult cortical morphology are implicated in various psychiatric disorders (Lyall et al., 2015) and cognitive decrements (Richetto and Riva, 2014, Markham et al., 2010, Richards et al., 2002, Richards et al., 2001), indication of a link between BW and adult cortical structure, in the population-based samples, could provide further evidence that prenatal growth is implicated in their aetiology. Furthermore, quantifying the role of early-life determinants of cortical structure could signpost prenatal modifiable risk factors to minimise detrimental effects on the cortex.

Preterm birth and IUGR are the leading causes of low and very low birth weight (LBW <2.5kg; VLBW <1.5kg) which are associated with impairments in cortical structure development that are apparent during the neonatal period (S. Miller et al., 2016, Kapellou et al., 2006). For individuals with LBW, VLBW or born small for gestational age, who underwent MRI between ages 6 and 19 years (*n* range = 55-157), lower BW was associated with lower global (De Bie et al., 2011, Martinussen et al., 2005) and regional surface area; predominantly in frontal and parietal gyri (Skranes et al., 2013). Lower global and regional volume has also been found in those with LBW compared to those born at term and appropriate for gestational age (De Bie et al., 2011, Taylor et al., 2011, Boardman et al., 2007, Martinussen et al., 2005). Conversely, those with LBW, have demonstrated regional thinning in some regions (e.g. parietal, temporal and occipital lobes) but thickening in others (e.g. frontal, cingulate and occipital lobes) (Bjuland et al., 2013, De Bie et al., 2011, Martinussen et al., 2005). Studies of LBW or VLBW individuals

compared to BW in the normal range have also found reduced cognitive ability, as defined by language and intelligence measures, in childhood (age range = 6 months-13 years old; *n* range = 64-53,000) and adulthood (Age = 18 years old; *n* = 161) (Goisis et al., 2017, Chaudhari et al., 2013, Torche and Echevarría, 2011, Ortiz-Mantilla et al., 2008, Tong et al., 2006); leading to an increased need for educational support (Johnson and Marlow, 2017, Johnson et al., 2009). Furthermore, LBW has also been identified as a risk factor for developing a spectrum of adult psychiatric disorders, including schizophrenia, autism and attention-deficit hyperactivity disorder (Lærum et al., 2017, Rubio-Abadal et al., 2015, Forsyth et al., 2013, Indredavik et al., 2004, Cannon et al., 2002, Geddes and Lawrie, 1995); with poorer cognitive ability also noted in these psychiatric populations (Lærum et al., 2017, Forsyth et al., 2013). Thus, extremes of low BW may influence adult brain cortical structure and inform developmental origins of cognitive difficulties and psychiatric disorders.

Although findings from LBW or VLBW populations have been informative, LBW affects around 7% in the UK population and outcomes are confounded by preterm birth, IUGR, placental insufficiency, and maternal medical conditions (Johnson et al., 2017); therefore the relationship between BW and brain structure/function for the general population with BW in the normal range (2.5-4.5kg (Goisis et al., 2017, Haukvik et al., 2014)) is uncertain. A small number of studies of appropriately grown individuals born at full term have reported links between subtle variations in BW and differences in brain structure later in life (Haukvik et al., 2014, Raznahan et al., 2012, Walhovd et al., 2012). Specifically, higher BW was associated with higher global cortical volume (Raznahan et al., 2012, Walhovd et al., 2012) and widespread higher surface area (Walhovd et al., 2012), including frontal, temporal and parietal lobes (Haukvik et al., 2014, Raznahan et al., 2012). Raznahan et al. (2012) (*n* = 450) also found a positive relationship between BW and global cortical thickness however, Haukvik et al. (2014) (*n* = 359) did not find an association with this metric. Such inconsistencies indicate that further testing of the relationship between BW and cortical structure, amongst individuals with normal BW, is required (Raznahan et al., 2012, Abel et al., 2010).

Within normal BW samples, higher BW has also been related with higher cognitive ability in childhood (aged 7-15 years) (Shenkin et al., 2004, Richards et al., 2001) and adulthood (aged 18 -79 years) (Grove et al., 2017), as well as higher cortical surface area, predominantly in the prefrontal cortex (Walhovd et al., 2016). Lower BW, within the normal range, has also been related to an increased risk for developing a range of psychiatric disorders (Abel et al., 2010) as well as lower surface area in individuals across the psychosis spectrum (Haukvik et al., 2014). Thus, the associations between normal variations in BW and brain structure may also be present across the life course and be a potential contributor to the development of cognitive and psychiatric disorders. However, with the exception of surface area (Walhovd et al., 2016), these BW and cortical morphology associations have only been formally tested in samples up to ~30 years old (Haukvik et al., 2014, Raznahan et al., 2012). Furthermore, there has been no formal testing of whether this is a causal relationship.

BW is influenced by both genetic and environmental factors (Gielen et al., 2008), with heritability estimates of between 26 and 30% from twin-based studies (Mook-Kanamori et al., 2012). Furthermore, up to 60 single nucleotide polymorphisms (SNPs) have been associated with BW at the level of genome-wide significance (Horikoshi et al., 2016, Horikoshi et al., 2013), explaining 2.0% (S.E ±1.1%) of the variance in BW and a genome-wide SNP-based heritability estimate of 15.1% (S.E ±0.9) (Horikoshi et al., 2016). BW-associated SNPs can be used as genetic instruments to test for a causal influence of BW (the exposure) on cortical structure (the outcome) and act as unconfounded proxies for BW across the lifespan. The current study used two-sample, Mendelian randomisation (MR) to test whether the BW-cortical structure association indicates a causal relationship between BW and cortical morphology. **Fig. 3.1** outlines the MR model and its assumptions - the Instrumental Variable (IV), consisting of SNPs robustly associated with the exposure (BW) is used to determine if the exposure causally affects the outcome (brain cortical structure). The current study identified 85 independent BW-associated SNPs. These SNPs were identified by performing a GWAS of BW in a UK Biobank (UKB) sample (excluding individuals with imaging data) larger than that utilised in previous BW GWAS (*n* = 201,586 compared to *n* = 143,677 (Horikoshi et al., 2016)).

Ideally, genetic variants, which have a robust and well understood biological effect on the trait, would be used as instruments to determine causation (Davey Smith and Hemani, 2014). However, individual SNPs for complex traits tend to have small effect sizes, and often make for weak instrument variables (Hagenaars et al., 2017). Using multiple SNPs can increase the predictive power of the instrument however, this can also increase the likelihood of pleiotropic effects occurring and, in turn, violate the MR assumptions (Hagenaars et al., 2017, Davey Smith and Hemani, 2014). MR Egger methods were used for sensitivity analyses, including tests of heterogeneity and horizontal pleiotropy, to test for any violations of these assumptions (see Davey Smith and Hemani, 2014).

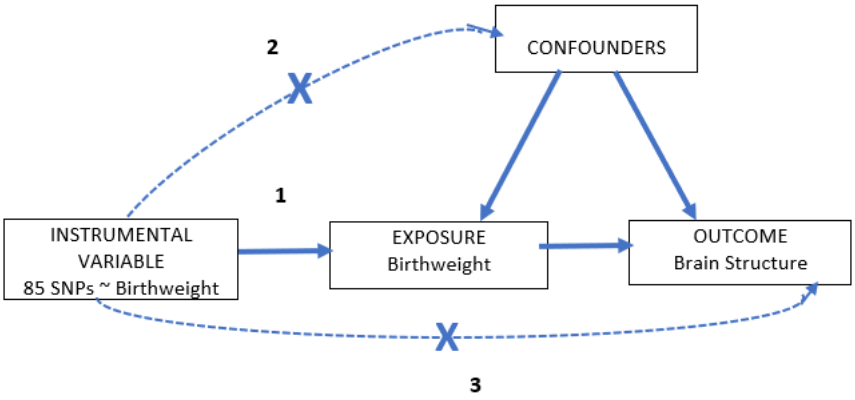

Fig. 3.1 Model outlining the assessed pathway for Mendelian Randomisation and its assumptions. MR analysis is subject to three assumptions; 1) there is an association between the genetic variants of the exposure and the exposure itself; 2) the genetic variants are independent of any confounding factors that are related to the association between the exposure and the outcome; and 3) the genetic variants are independent of the outcome and therefore can only be associated with the outcome by operating through the exposure (this is also known as the exclusion restriction) (Bowden et al., 2016). Path numbers 1, 2 and 3 in the figure correspond to these assumptions. Adapted from Bowden *et al.* (Bowden et al., 2016).

The current study therefore extends the current literature by testing 1,680 individuals over 45 years old for associations between BW (in a population-based sample) and brain cortical volume, surface area and thickness (both globally and regionally). Notably, as we are treating BW as a continuous as opposed to a dichotomous variable, we are increasing its statistical power. Furthermore, testing of BW in the normal range, allows for results to be more generalisable to the whole population. Lastly, the application of MR to formally determine if this relationship is causal is a novel approach to this question. We hypothesised phenotypic

associations between BW and cortical structure whereby higher BW would be linked with larger global cortical volume and global and regional surface area (particularly in frontal, temporal and parietal regions), and that these associations would be indicative of a causal relationship. No hypotheses of cortical thickness were made due to inconsistency of findings in the literature.

3.5 Methods

3.5.1 Participants Detailed participant information has been reported previously (Cox et al., 2016) (http://www.ukbiobank.ac.uk/participants/), see **Appendix B3.1.1** (p21-22)**.** The current sample included white British, individuals with complete genetic, cortical and BW data, for three cortical parameters; cortical volume, surface area and thickness. Only individuals who reported to not be part of a multiple birth were included (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1777). Furthermore, global cortical outliers (±3 S.Ds), were removed for all three cortical parameters, resulting in a current sample of 1,680 individuals ($n_{males}/n_{females}$ = 703/977; mean age at time of scan = 60.76 years, S.D = ±7.40 years, range = 46-78 years) (Reus et al., 2017, Shen et al., 2017). We note here that the UKB sample is not considered to be representative of the general population, due to evidence of a 'healthy volunteer' selection bias however, it can still be used to scientifically infer possible exposure ~ health outcome associations that may be generalised to wider populations (Fry et al., 2017). Ethical approval for UKB was received from the research ethics committee (REC reference 11/NW/0382) under application 4844. Informed consent was provided from all participants (see http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200).

3.5.2 Imaging Procedures UKB imaging details are described in full elsewhere (Alfaro-Almagro et al., 2017, Cox et al., 2016, K. Miller et al., 2016), https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). In summary, images were acquired on a single 3T Siemens Skyra scanner. Structural brain images were acquired in the sagittal plane using a T1-weighted, three-dimensional, magnetization-prepared rapid gradient-echo sequence at a resolution of 1×1×1mm with a field of view of 208×256×256. Further information

on the imaging protocol (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367) and imaging acquisition parameters (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977) are documented online. Brain scans were anonymised at the time of acquisition and were processed locally on a server cluster at the Centre for Cognitive Ageing and Cognitive Epidemiology (CCACE, http://www.ccace.ed.ac.uk/), in Edinburgh using FreeSurfer (v5.3, http://surfer.nmr.mgh.harvard.edu/).

3.5.3 MRI Analysis We processed the T1-W volumes from the first UKB imaging release locally to derive cortical measures of thickness (mm), surface area (mm^2) and volume (mm^3), for further details see **Appendix B3.1.2** (p22-24)**.** Briefly, parcellation of cortical structures was conducted in FreeSurfer v5.3 using the Desikan-Killiany neuroanatomical atlas (Desikan et al., 2006). This generated 34 bilateral cortical parcels that can be attributed to eight lobar structures, each with volume, surface area and mean thickness measures (Desikan et al., 2006). Eleven parcels were combined into four larger regions as previously described (Cox et al., 2017, Klein and Tourville, 2012); resulting in 27 bilateral regions of interest (ROIs) which were assigned to one of nine lobar regions, see **Appendix B3.1.2** (p22-24)**.** The X, Y and Z co-ordinates of the centre of the brain mask within the scanner (http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25756, http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25757, http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25758) were also fitted as covariates for the current analyses to account for varying head positions in the scanner; see **Appendix B3.1.3** (p24-25) for further information on these variables.

3.5.4 MRI Quality Control Procedures Quality checks were conducted on the success of processing on all scans. T1-weighted images were initially carried out by UKB (Brain Imaging Documentation V1.1, http://www.ukbiobank.ac.uk, Alfaro-Almagro et al., 2018) with further Quality Control (QC) procedures conducted locally. For local QC procedures see (Cox et al., 2017) and http://enigma.ini.usc.edu/protocols/imaging-protocols/), images were visually assessed for major errors (e.g. zero or partial output, substantial skull strip issues or tissue

identification issues) which removed 458 scans, see **Appendix B Fig. B3.1** (p22). The remaining 3,875 scans were then assessed for minor errors (e.g. erroneous boundary placement, minor skull stripping issues and minor tissue omission) which resulted in removal of individual regions within scans (6,192 of the possible 295,052 regions were removed). As global information was largely unaffected by the FreeSurfer reconstruction process, global and lobar values were extracted from the data with major errors removed but did not undergo QC exclusion for minor errors. However, exclusion of global cortical outliers (±3 S.D.s) provided a further internal imaging QC as in previous publications (Reus et al., 2017, Shen et al., 2017).

3.5.5 Measure of Birth Weight Participants were asked to provide their own BW information. Recalled BW has been shown to have high agreement with recorded BW (r = .90) and considered a valid and suitable measure for epidemiological studies (Shenkin et al., 2017). BW data were collected at initial assessment and at the first repeat assessment (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20022). As information from both instances were comparable (r = .94), the BW variable included data from instance one as default, NA values from instance one were replaced by data from instance two. The BW range in the current sample was .91-5.78kg (mean = 3.39kg, S.D = ± .61kg). Participant numbers were calculated for ***normal*** (2.5-4.5kg (Haukvik et al., 2014, Goisis et al., 2017)) *n* = 1,471 (87.56%); ***LBW*** (1.5-2.5kg) *n* = 116 (6.90%); ***VLBW*** (<1.5kg) *n* = 8 (0.48%); and ***high BW*** (>4.5kg) *n* = 85 (5.06%) ranges. As the aim of the current study was to analyse BW range in the general population, the initial analyses used the full range of BW information. However, further analyses were conducted to determine if the same patterns occurred in the normal BW range only.

3.5.6 Covariates *Socioeconomic Deprivation* was measured using the Townsend deprivation index (range = -6.26 – 9.16, mean = -2.04, S.D = ±2.63), calculated when the participant joined the UKB study. Individuals were assigned a score based on census output regarding their postcode (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=189). *Standing height* was measured using a Seca 202 device (range = 143 – 194cm, mean = 169.14cm, S.D = ±9.32cm)

and was collected at initial assessment, first repeat assessment and at time of scan (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=50), data from both instances were comparable (r = .99). As with BW, data from the first instance was used by default and missing values from instance one were replaced by data from instance two.

3.5.7 Statistical Analysis - Phenotypic Associations All phenotypic analyses were conducted in R (v3.2.3) using a linear mixed effects (LME) model in package "nlme" (v3.1-127, Pinheiro et al., 2017), to determine whether cortical structures were associated with BW. LME models were first conducted in a repeated measures format with hemisphere fitted as a random factor. Analyses were also conducted to determine if there was a BW × hemisphere interaction which would require testing as an independent measure. This process was repeated for participants within the normal BW range (2.5 - 4.5kg) to test for associations that could not be skewed by extreme BW values.

For regions that resulted in significant interactions ($P < .05$), analyses were conducted with an independent measure design using linear regression models without hemisphere as a covariate and reported as two separate structures in the results section.

An LME model was tested across the full and normal BW range. This model included age, age^2, sex and X, Y and Z co-ordinates of the brain mask within the scanner, height, Townsend deprivation index, and 15 principal components (see **Appendix B3.1.3,** p24-25), to account for population stratification (Bycroft et al., 2017), as fixed effects.

Intracranial volume (ICV) was also included as a fixed effect for lobar and parcellation analyses to control for the size of specific regions relative to the whole brain. This measure of ICV was derived based on a UKB imaging derived phenotype (IDP), similar to that calculated by Statistical Parametric Mapping methods (https://www.fil.ion.ucl.ac.uk/spm/) whereby grey matter, white matter and ventricular cerebral spinal fluid are added together. Although this measure is different to traditional measures of ICV (e.g. FreeSurfer; https://surfer.nmr.mgh.harvard.edu/fswiki/eTIV), the authors do not expect this covariate to make any substantial changes to the results for two reasons. Firstly, this measure is highly correlated with the Volumetric scaling from T1 head image to standard space

(http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=25000) available in UKB (r = .898) and secondly, this measure has been validated in previous studies (e.g. Ritchie et al., 2018, Shen et al., 2017).

Here we only report statistically significant associations (P < .05) between BW and cortical brain structure from these models however, results for all other regions can be found in **Appendix B3.2.1.2** (p32-47). In line with previous studies, we also tested a Base model for both the whole and normal BW range which did not include additional covariates (see ***Covariates***) (Haukvik et al., 2014, Raznahan et al., 2012). See **Appendix B3.1.5** (p25-26) for further details.

Standardised regression coefficients are reported throughout. Utilising the 'p.adjust' function in R ('stats' package v3.2.3), the false discovery rate (FDR) method, with a rate of P < .05 (Genovese et al., 2002), was used to correct lobar and parcellation results for multiple comparisons.

3.5.8 Genotyping and Imputation Processing Procedures for genotyping, imputation and quality control for UKB have been reported previously (Howard et al., 2018, Luciano et al., 2018, Bycroft et al., 2017, Wain et al., 2015). Briefly, 488,377 blood samples were assayed using two different genotyping arrays; Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (Wain et al., 2015) and Applied Biosystems UKB Axiom Array (http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UK-Biobank-Axiom-Array-Content-Summary-2014.pdf). Further information on these arrays can be found in **Appendix B3.1.4** (p25).

Genetic QC was performed using the approach described by Howard et al. (2018). Firstly, participants were excluded based on shared genetic relatedness up to the third degree using kinship coefficients (>.044) identified using the KING toolset (Manichaikul et al., 2010), as previous (Howard et al., 2018, Bycroft et al., 2017). To maximise the sample, we subsequently added back in one member from each group of related individuals, using a genomic relationship matrix, and selected only those with a relatedness of less than .025 with any other individual. Individuals were also excluded based upon a combination of both self-reported

ethnicity and a PC analysis (see **Appendix B, p22 and 24**) which revealed individuals with similar ancestral backgrounds. The final QC exclusion criteria included variant missing-ness per individual (>2%), gender mismatch, variant call rate (<98%), Hardy-Weinberg equilibrium ($P < 10^{-6}$), minor allele frequency < .01, an imputation quality < .1, resulting in 331,374 individuals and 7,730,951 variants.

3.5.9 Instrumental Variable – Exposure We conducted a GWAS of BW using the UKB BGENIE pipeline (Bycroft et al., 2017), in order to identify genome wide significant, BW-associated SNPs. This analysis was conducted using a subset of the UKB sample, independent from those with imaging data used in the, phenotypic, cortical brain structure ~ BW association analysis and excluded individuals who were part of a multiple birth (n = 201,586, see **Appendix B, Fig. B3.3,** p48). Genome-wide SNP-based heritability for BW estimated in this sample was 10% (S.E ±0.5%). In order to identify independently-associated BW SNPs we utilised Functional Mapping and Annotation of genetic associations software (FUMA, http://fuma.ctglab.nl/, Watanabe et al., (2017)), resulting in the identification of 114 genome wide significant SNPs ($P < 5\times10^{-8}$) with a MAF > 0.01 and HWE $P < 1\times10^{-6}$. Clump-based linkage disequilibrium (LD) pruning was performed with a R^2 of < 0.1 within a 250kb window. See **Fig. 3.2, Table 3.1.** These 114 SNPs explained 3% of the variance of BW in UKB, as calculated by the formula in Shim et al. (2015).

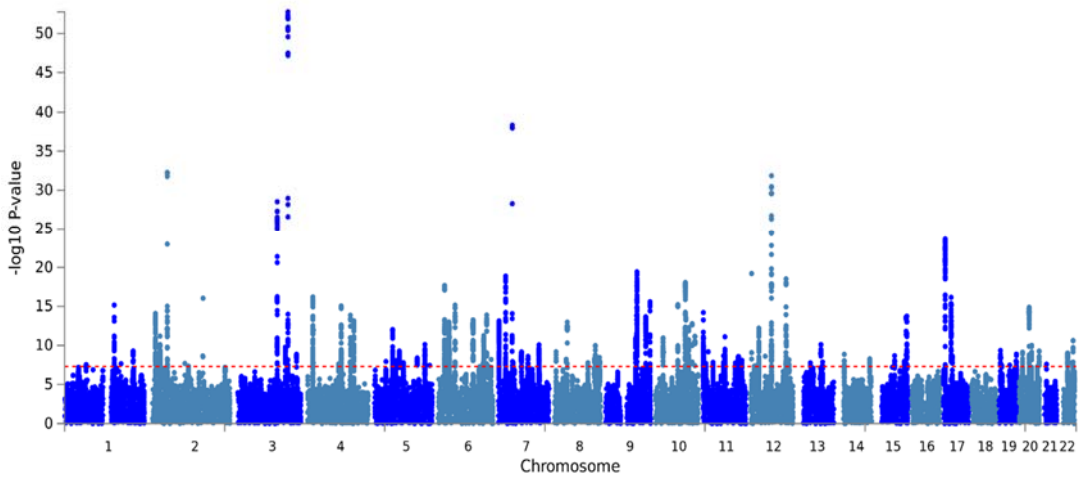

Fig. 3.2 Manhattan plot of independently associated birth weight SNPs identified using FUMA (Watanabe et al., 2017)

Additional quality control of the data was conducted using the 'clump_data' and 'harmonise_data' functions in the 'TwoSampleMR' (Hemani et al. 2018) package for R (v0.4.5) to ensure that the exposure and the outcome effects were on the same reference allele and no SNPs were in LD with each other. This resulted in the removal of an additional 27 SNPs with R^2 > 0.001 as well as two SNPs which were palindromic with intermediate allele frequencies. The current IV therefore consisted of 85 SNPs (see **Table 3.1)**

Table 3.1 85 Birth weight associated single nucleotide polymorphisms (SNPs) used in the current study

	Genome-wide Significant SNPs	Annotated Gene	Chr	E.A	Non E.A	E.A Freq	UKB Freq	HWE	Effect Size	S.E	p
1	rs13322435	LINC02029	3	G	A	0.404	0.411	0.240	-0.047	0.003	$1.69\times^{-53}$
2	rs1374205	-	2	C	T	0.700	0.692	0.007	0.041	0.003	$5.20\times^{-33}$
3	rs7306710	-	12	C	T	0.519	0.528	0.210	-0.036	0.003	$1.42\times^{-32}$
4	rs11708067	ADCY5	3	G	A	0.243	0.239	0.712	0.039	0.003	$3.04\times^{-29}$
5	rs222857	ELP5/CLDN7	17	T	C	0.571	0.565	0.363	0.031	0.003	$2.27\times^{-24}$
6	rs145965565	PTCH1	9	G	T	0.095	0.091	0.206	0.047	0.005	$3.84\times^{-20}$
7	rs34776209	IGF2BP3	7	T	C	0.248	0.244	0.986	-0.031	0.003	$1.35\times^{-19}$
8	rs3184504	SH2B3	12	C	T	0.518	0.537	0.399	0.027	0.003	$3.08\times^{-19}$
9	rs11187141	-	10	T	A	0.376	0.378	0.706	0.027	0.003	$8.87\times^{-19}$
10	rs9368222	CDKAL1	6	A	C	0.262	0.261	0.641	-0.030	0.003	$2.11\times^{-18}$
11	rs979532	LCORL	4	T	C	0.739	0.741	0.574	-0.028	0.003	$6.40\times^{-17}$
12	rs9909342	-	17	A	G	0.383	0.391	0.793	0.026	0.003	$7.13\times^{-17}$
13	rs28429551	GPSM1	9	A	T	0.755	0.758	0.703	-0.028	0.003	$2.59\times^{-16}$
14	rs9645500	HKDC1	10	G	T	0.693	0.681	0.020	0.026	0.003	$6.12\times^{-16}$
15	rs7744700	-	6	A	T	0.292	0.289	0.578	-0.027	0.003	$7.05\times^{-16}$
16	rs2047408	TET2	4	C	G	0.669	0.670	0.402	-0.026	0.003	$8.87\times^{-16}$
17	rs11698914	COMMD7	20	G	C	0.771	0.764	0.481	-0.029	0.004	$1.31\times^{-15}$
18	rs72851023	-	11	T	C	0.076	0.074	0.657	0.044	0.006	$6.22\times^{-15}$
19	rs12692386	ADAM17	2	G	A	0.672	0.674	0.404	0.025	0.003	$8.11\times^{-15}$
20	rs7772579	ESR1	6	C	A	0.277	0.277	0.743	-0.026	0.003	$1.31\times^{-14}$
21	rs7402983	IGF1R	15	C	A	0.601	0.605	0.429	-0.024	0.003	$1.82\times^{-14}$
22	rs2793003	RC3H2	9	C	T	0.855	0.843	0.436	-0.032	0.004	$2.19\times^{-14}$
23	rs12206634	SESN1	6	A	G	0.121	0.121	0.992	0.035	0.005	$5.31\times^{-14}$
24	rs2131354	HHIP	4	A	G	0.528	0.518	0.354	0.022	0.003	$7.06\times^{-14}$
25	rs798528	GNA12/AMZ1	7	C	A	0.305	0.299	0.580	-0.024	0.003	$7.31\times^{-14}$
26	rs9394201	SMIM29	6	T	C	0.840	0.833	0.953	-0.030	0.004	$1.03\times^{-13}$

27	rs515071	ANK1	8	G	A	0.761	0.762	0.364	0.026	0.004	$1.06\times^{-13}$
28	rs1801253	ADRB1	10	C	G	0.737	0.732	0.289	0.025	0.003	$1.68\times^{-13}$
29	rs12205495	TULP1	6	A	T	0.218	0.212	0.384	0.026	0.004	$3.64\times^{-13}$
30	rs10883846	-	10	T	C	0.394	0.386	0.171	-0.022	0.003	$5.09\times^{-13}$
31	rs2291261	ITPR2	12	A	G	0.488	0.478	0.897	-0.022	0.003	$6.18\times^{-13}$
32	rs11739073	-	5	A	T	0.155	0.155	0.325	-0.029	0.004	$9.38\times^{-13}$
33	rs12713004	KLHL29	2	G	A	0.726	0.720	0.258	0.023	0.003	$6.49\times^{-12}$
34	rs905938	ZBTB7B	1	C	T	0.265	0.261	0.689	0.023	0.003	$7.05\times^{-12}$
35	rs667515	-	11	C	G	0.386	0.382	0.197	-0.021	0.003	$7.93\times^{-12}$
36	rs4748981	-	10	C	A	0.669	0.672	0.191	-0.022	0.003	$1.13\times^{-11}$
37	rs768056	-	9	T	C	0.177	0.178	0.276	0.027	0.004	$1.33\times^{-11}$
38	rs1135856	PRR34	22	C	T	0.292	0.284	0.816	-0.022	0.003	$2.39\times^{-11}$
39	rs12656357	-	5	A	T	0.217	0.214	0.160	-0.024	0.004	$7.71\times^{-11}$
40	rs7336104	-	13	T	C	0.178	0.176	0.382	-0.026	0.004	$7.82\times^{-11}$
41	rs6467157	SND1	7	C	T	0.295	0.289	0.734	-0.022	0.003	$8.59\times^{-11}$
42	rs6513671	-	20	G	A	0.383	0.382	0.777	0.020	0.003	$1.00\times^{-10}$
43	rs12675643	-	8	A	T	0.237	0.241	0.088	0.023	0.004	$1.06\times^{-10}$
44	rs4681161	CPA3	3	C	T	0.559	0.546	0.390	-0.019	0.003	$1.70\times^{-10}$
45	rs2779165	UHRF1	19	C	G	0.813	0.819	0.691	-0.024	0.004	$4.48\times^{-10}$
46	rs3754140	PROX1	1	C	T	0.262	0.260	0.986	0.021	0.003	$5.23\times^{-10}$
47	rs817329	ZNF512B	20	G	T	0.595	0.593	0.820	-0.019	0.003	$5.30\times^{-10}$
48	rs2042874	LHFPL2	5	G	A	0.432	0.426	0.010	0.019	0.003	$5.34\times^{-10}$
49	rs62496915	MCPH1	8	G	C	0.117	0.118	0.379	0.029	0.005	$6.52\times^{-10}$
50	rs80089232	MLXIPL	7	C	T	0.070	0.066	0.335	0.036	0.006	$6.92\times^{-10}$
51	rs5762980	KREMEN1	22	G	A	0.651	0.652	0.383	-0.019	0.003	$1.00\times^{-09}$
52	rs255773	LILRB3	19	T	C	0.465	0.460	0.028	-0.018	0.003	$1.31\times^{-09}$
53	rs12889267	ARHGEF40	14	G	A	0.167	0.164	0.325	-0.024	0.004	$1.39\times^{-09}$
54	rs9827156	KLHL24	3	A	G	0.261	0.273	0.225	-0.021	0.003	$1.40\times^{-09}$
55	rs339969	RORA	15	A	C	0.615	0.618	0.959	0.018	0.003	$2.06\times^{-09}$
56	rs7941126	MAP3K11/KCNK7	11	G	A	0.504	0.500	0.029	-0.018	0.003	$2.13\times^{-09}$
57	rs9669403	-	12	A	G	0.401	0.404	0.368	0.018	0.003	$2.44\times^{-09}$

58	rs13231861	CALCR	7	G	A	0.451	0.442	0.250	0.018	0.003	$2.55\times^{-09}$
59	rs57414412	-	11	A	G	0.288	0.286	0.133	-0.020	0.003	$2.72\times^{-09}$
60	rs13257363	SLC45A4	8	A	G	0.411	0.404	0.139	-0.018	0.003	$3.52\times^{-09}$
61	rs1476096	-	5	C	A	0.581	0.590	0.073	0.018	0.003	$4.05\times^{-09}$
62	rs74819596	DLK1	14	T	C	0.108	0.104	0.453	-0.028	0.005	$5.30\times^{-09}$
63	rs3217870	CCND2	12	T	C	0.606	0.609	0.004	-0.018	0.003	$5.51\times^{-09}$
64	rs2934844	PDE10A	6	T	A	0.670	0.678	0.332	0.019	0.003	$6.32\times^{-09}$
65	rs3806315	PTPN14	1	A	G	0.594	0.577	0.347	0.018	0.003	$8.20\times^{-09}$
66	rs55863716	-	11	A	G	0.264	0.263	0.101	0.020	0.003	$8.29\times^{-09}$
67	rs6873192	PIK3R1	5	G	A	0.516	0.523	0.492	-0.017	0.003	$9.27\times^{-09}$
68	rs116849452	ZNF888	19	G	C	0.056	0.054	0.840	-0.038	0.007	$1.00\times^{-08}$
69	rs4932373	FURIN	15	C	A	0.325	0.319	0.745	-0.018	0.003	$1.05\times^{-08}$
70	rs12656216	SKP2	5	A	G	0.786	0.768	0.007	0.021	0.004	$1.16\times^{-08}$
71	rs6971880	-	7	A	T	0.064	0.072	0.744	-0.035	0.006	$1.41\times^{-08}$
72	rs10741669	KCNQ1	11	A	G	0.880	0.880	0.309	0.026	0.005	$1.43\times^{-08}$
73	rs5030317	WT1	11	G	C	0.267	0.286	0.024	-0.019	0.003	$1.49\times^{-08}$
74	rs6930558	-	6	T	G	0.745	0.750	0.270	0.020	0.003	$1.58\times^{-08}$
75	rs7724489	-	5	T	A	0.874	0.866	0.227	-0.025	0.005	$1.63\times^{-08}$
76	rs7016987	ZFPM2	8	T	C	0.194	0.206	0.254	0.021	0.004	$1.65\times^{-08}$
77	rs9603672	-	13	A	G	0.888	0.874	0.774	-0.027	0.005	$1.73\times^{-08}$
78	rs4320142	STPG2	4	G	T	0.248	0.248	0.641	0.019	0.003	$2.34\times^{-08}$
79	rs2229742	NRIP1	21	C	G	0.104	0.100	0.125	-0.027	0.005	$2.56\times^{-08}$
80	rs975451	SLC35D1	1	C	T	0.734	0.741	0.587	-0.019	0.003	$2.86\times^{-08}$
81	rs118106744	-	12	T	C	0.054	0.052	0.011	-0.036	0.007	$3.34\times^{-08}$
82	rs41355649	CEBPA	19	A	G	0.068	0.065	0.251	-0.033	0.006	$3.40\times^{-08}$
83	rs2918307	-	19	G	A	0.153	0.154	0.200	-0.023	0.004	$3.85\times^{-08}$
84	rs1014448	-	12	T	C	0.927	0.927	0.377	0.033	0.006	$4.45\times^{-08}$
85	rs62157841	TMEM87B	2	A	G	0.394	0.386	0.012	-0.017	0.003	$4.61\times^{-08}$

Chr = chromosome, SNPs were annotated to genes using the Ensembl Variant Effect Predictor (McLaren et al., 2016),
A positive effect size means that the effect allele for the SNP increases BW whereas a negative effect size means that the effect allele for the SNP decreases BW. The directions of these effects are accounted for in the MR analysis.

3.5.10 Instrumental Variable – Outcome The same UKB BGENIE pipeline (Bycroft et al., 2017), as described above in relation to the IV-exposure, was utilised to conduct GWAS for cortical structures in a subset of the UKB sample with imaging data, independent from that of the sample used to perform the BW GWAS (*n* = 2,913). This sample is larger than that used for the phenotypic analysis as it was not restricted to individuals who also had BW data. The same summary statistics (major and minor alleles for each SNP, allele frequencies, beta coefficients, *p*-values and S.E) were extracted in order to form an IV-exposure for each of the cortical regions.

3.5.11 Statistical Analysis - Two-Sample Mendelian Randomization Two-sample MR analysis was conducted as described in previous publications (Noyce et al., 2017, Bowden et al., 2016, Bowden et al., 2015) and as outlined below. This was applied on a region of interest (ROI) basis, where only cortical structures which were significantly phenotypically associated ($P < .05$) with BW (see ***Phenotypic Associations***) were tested. We conducted a two-sample, Inverse-Variance Weighted (IVW) regression analysis using the MR Base R package 'TwoSampleMR' (v0.4.5, https://mrcieu.github.io/TwoSmpleMR/). This analysis uses an Instrumental Variable (IV) which consisted of the 85 BW-associated SNPs, identified above. The IVW method performs a regression of two vectors (IV-exposure ~ IV-outcome) with the intercept constrained to zero; constraining the intercept to zero makes the assumption that all variants (SNPs) are valid IVs. Weighting the association by standard error allows correction for minor allele frequency (see Bowden et al. (2016)). MR analyses were also corrected for multiple comparison using FDR (R 'stats' package v3.2.3), with a rate of $P = .05$. 'Single SNP' and 'leave-one-out' sensitivity analyses were conducted to determine if a single variant was producing disproportionate effects, using the IVW method. To ensure that the third MR assumption was not violated (that the IVs are valid, showing no evidence of heterogeneity or horizontal pleiotropy) we used the 'mr_heterogeneity' and 'mr_pleiotropy' functions in the 'TwoSampleMR' package. Heterogeneity was tested using IVW Cochran's *Q,* with a P-value > 0.05 suggesting a lack of heterogeneity. To test for pleiotropy, we used the MR-Egger intercept. In MR-Egger regression the intercept is not constrained to zero but is otherwise

similar to IVW regression. An intercept that is significantly different from zero in MR-Egger regression ($P < .05$) would suggest pleiotropic effects which will bias the IVW estimate (Noyce et al., 2017).

3.6 Results

3.6.1 Demographics In the current sample, BW was tested using the whole range within the population-based sample (n = 1,680) as well as individuals within the normal BW range (n = 1,471). **Fig. 3.3** shows the distributions of the two BW ranges.

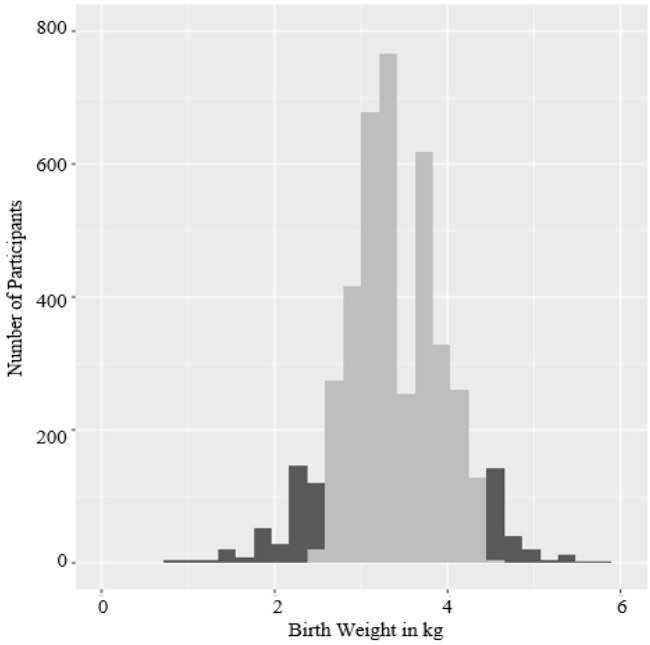

Fig. 3.3 Distribution of birth weight in kg Graph showing the distribution of the whole birth weight range in kg (dark grey and light grey areas combined, n = 1,680) where the light grey area represents BW in the normal range (n = 1,471)

BW was significantly associated with sex (whole BW range: $X^2 = 89.376$, $p < 2.20\times10^{-16}$; normal BW range: $X^2 = 76.368$, $p < 2.20\times10^{-16}$); males had higher BW than females, and height (whole BW range: $r = .267$, $p < 2.20\times^{-16}$; normal BW range: $r = .218$, $p < 2.20\times10^{-16}$); taller individuals had higher BW, see **Table 3.2**. No significant associations were found between BW and age at scan (whole BW range: $r = -.005$, $p = .775$; normal BW range: $r = -.008$, $p = .678$) or Townsend deprivation score (whole BW range: $r = .016$, $p = .340$; normal BW range: $r = .025$, $p = .176$).

Table 3.2 Descriptive statistics for demographic variables and their associations with birth weight

	Whole BW range (n = 1,680)				*Normal BW range (n = 1,471)*			
	Range	**Mean**	**S.D**	**Statistics**	**Range**	**Mean**	**S.D**	**Statistics**
Sex	-	-	-	$X^2 = 89.376$, p < 2.20×10^{-16}***	-	-	-	$X^2 = 76.368$, *p* < 2.20×10^{-16}***
Male	0.91 – 5.78	3.50	0.61	-	2.52 – 4.45	3.48	0.41	-
Female	0.96 – 5.44	3.31	0.59	-	2.52 – 4.45	3.38	0.42	-
Height	143 - 194	169.14	9.32	*r* = .267, *p* < 2.20×10^{-16}***	143 - 194	169.18	9.18	*r* = .218, *p* < 2.20×10^{-16}***
Age at time of scan	46 - 78	60.76	7.40	*r* = -.005, *p* = .775	46.08 – 77.83	60.62	7.41	*r* = -.008, *p* = .678
Townsend Deprivation Scale	-6.26 – 9.16	-2.04	2.63	*r* = .016, *p* = .340	-6.26 – 9.16	-2.08	2.59	*r* = .025, *p* = .176

***$p_{corr} \leq .001$, **$p_{corr} \leq .01$, *$p_{corr} \leq .05$, · $p_{corr} \leq .10$,
Mean and S.D values relating to males and females within the samples refer to mean and standard deviations of birth weight in kg.

3.6.2 Associations Between Birth Weight and Cortical Structure Results for BW × hemisphere interactions on cortical structure can be found in **Appendix B3.2.1.1** (p27-31). Results for regions with significant interactions are reported below as independent left and right structures.

3.6.2.1 Cortical volume: There was a significant positive association between cortical volume and BW globally (β = .104, p = 2.86×10^{-07}, R^2 = .011) for three lobes (β range = .041, .052, p_{corr} = .009), and two out of the three individual parcels (β range = .070, .068, p_{corr} range = .028, .009); higher BW was related to larger cortical volumes in these regions. However, higher BW was associated with lower volume of the left lateral occipital parcel (β = -.059, p_{corr} = .028, R^2 = 0.004). (See **Table 3.3**, **Fig. 3.4)**. Results using a Base model to test these associations were largely similar, see **Appendix B3.2.1.2** (p33-36)**.**

3.6.2.2 Cortical surface area: Higher BW was associated with higher global surface area (β = .100, p = 3.58×10^{-07}, R^2 = .010) along with the insular (β = .041, p_{corr} = .044) and parietal (β = .037, p_{corr} = .037) lobes, and several individual parcels (β range = .056 - .069, p_{corr} range = .035 - .010), including the middle temporal (β = .069, p_{corr} = .010) medial orbitofrontal (β = .056, p_{corr} = .032) and inferior frontal gyrus (IFG) (β = .059, p_{corr} = .035). See **Table 3.3.**

3.6.2.3 Cortical thickness: No association was found between BW and global cortical thickness. However, negative associations were found between BW and the lateral occipital parcel (β = -.097, p_{corr} = .005); in this region, higher BW was related to a thinner cortex.

Table 3.3 Significant associations (P_{corr} < .05) between birth weight and cortical structure using the whole birth weight range

Brain Measure	Effect Size	S.D	p value	p_{corr}	R^2
Cortical Volume					
Global	0.104	0.020	2.86×10^{-07}***	-	0.011
Lobes					
Insula	0.049	0.017	0.003	0.009**	0.002
Parietal	0.041	0.013	0.002	0.009**	0.002
Postcentral	0.052	0.017	0.002	0.009**	0.003
Parcellations					
Left Lateral Occipital	-0.059	0.020	0.003	0.028*	0.004
Middle Temporal	0.068	0.020	0.001	0.009**	0.005
Supramarginal	0.070	0.020	0.001	0.009**	0.005
Cortical Surface Area					
Global	0.100	0.020	3.58×10^{-07}***	-	0.010
Lobes					
Insula	0.041	0.016	0.011	0.044*	0.002
Parietal	0.037	0.013	0.005	0.037*	0.001
Parcellations					
Medial Orbitofrontal	0.056	0.019	0.003	0.032*	0.003
Middle Temporal	0.069	0.019	$3.50\times^{-04}$	0.010*	0.005
Supramarginal	0.059	0.020	0.003	0.032*	0.004
Inferior Frontal Gyrus	0.059	0.021	0.005	0.035*	0.003
Cortical Thickness					
Parcellations					
Lateral Occipital	-0.097	0.026	1.70×10^{-04}	0.005**	0.009

***$p_{corr} \leq .001$, **$p_{corr} \leq .01$, *$p_{corr} \leq .05$, . $p_{corr} \leq .10$.
Associations between birth weight and cortical volume, surface area and thickness n = 1,680). For clarity, only significant associations are reported here and left and right entries are displayed for regions with significant birthweight × hemisphere interactions

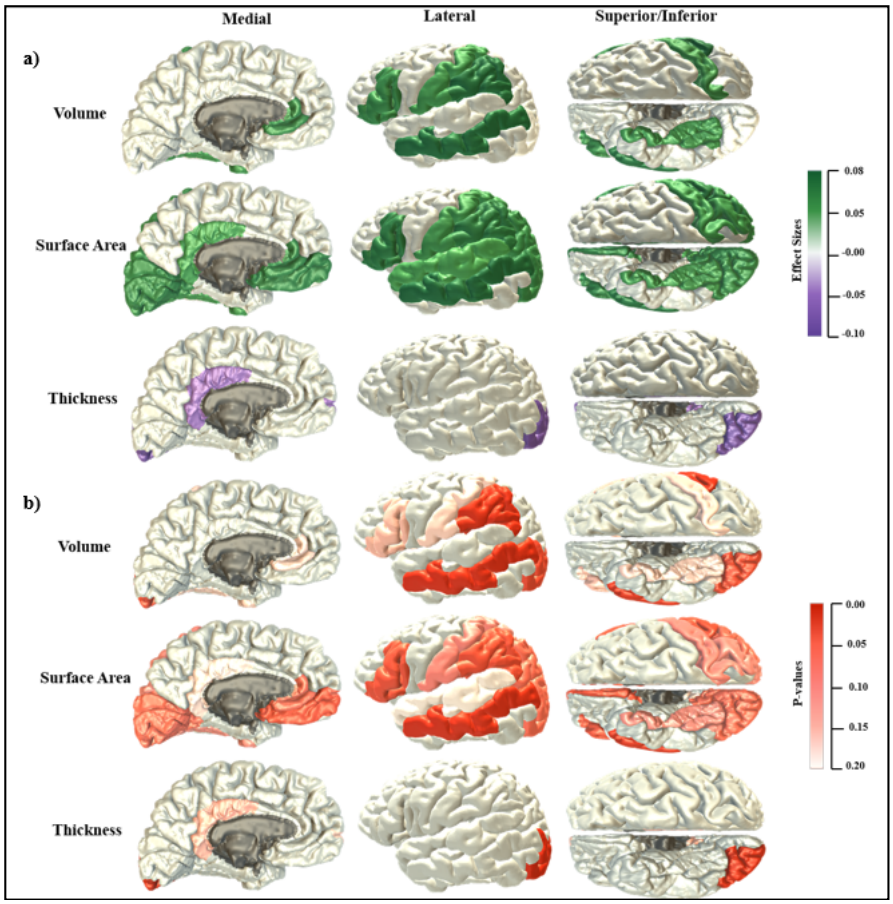

Fig. 3.4 Effect sizes and corrected p values for cortical parcellations Figures depicting a) effect sizes (standardised beta) and b) corrected p values for associations between the whole range of BW and cortical volume, surface area and thickness (n = 1,680), for each cortical parcellation

3.6.3 Associations Between Birth Weight (Within the Normal Range) and Cortical Structure No hemisphere interactions were found with normal BW on brain cortical structure.

3.6.3.1 Cortical volume: Higher BW was related to larger cortical volumes globally (β = .097, $p_{corr} = 5.64\times10^{-06}$, R^2 = .009) but not in individual lobes and parcels. See **Table 3.4**.

3.6.3.2 Cortical surface area: Higher BW was associated with larger global surface area (β = .088, $p = 2.60\times10^{-05}$, R^2 = .008) but not individual lobes and parcels.

3.6.3.3 Cortical thickness: No association was found between normal BW and global cortical thickness. However, a positive association between BW and the precentral lobe was found (β = .074, p_{corr} = .018) suggesting that higher BW was related to higher thickness in this area. See **Table 3.4.**

Table 3.4 Significant associations (P_{corr} < .05) between birth weight and cortical structure using the normal birth weight range

Brain Measure	Effect Size	S.D	p value	p_{corr}	R^2
Cortical Volume					
Global	0.097	0.021	5.64×10^{-06}***	-	0.009
Cortical Surface Area					
Global	0.088	0.021	2.60×10^{-05}***	-	0.008
Cortical Thickness					
Lobes					
Precentral	0.074	0.024	0.002	0.018*	0.005

***$p_{corr} \leq .001$, **$p_{corr} \leq .01$, *$p_{corr} \leq .05$, . $p_{corr} \leq .10$,
Significant associations between normal ranges of birth weight and cortical volume, surface area and thickness (*n* = 1,471)

3.6.4 Mendelian Randomisation Applying an ROI approach, the aforementioned brain structures which were significantly associated with BW in the whole BW range, were also analysed using an MR model to determine any causal effects of BW on cortical structures, see **Table 3.5.** The Two-sample, IVW regression analysis revealed evidence of a significant causal effect of BW on insular lobe cortical volume (β = .346, p_{corr} = .009). There was also a significant causal effect of BW on global (β = .281, p_{corr} = .009) as well as the insular lobe (β = .371, p_{corr} = .005), medial orbitofrontal (β = .417, p_{corr} = .006), middle temporal (β = .287, p_{corr} = .045) and IFG (β = .512, p_{corr} = .045) parcel cortical surface area. Another association between BW and parietal lobe cortical surface area was also found but was only nominally significant when correcting for multiple testing (β = .224, p_{corr} = .068). No evidence of heterogeneity was found for any region (Q, $P > 0.05$) nor was there any indication of horizontal pleiotropy (MR Egger Intercept, $P > 0.05$); see **Table 3.5.** Furthermore, 'leave one out' analyses suggested that IVW results were not driven by an individual SNP and that each of these genetic variants were symmetrically distributed around the IVW point estimate. Graphical representations of these sensitivity analyses can be found in **Appendix B3.2.4.1** (p51-63)**.** We therefore accepted the IVW results which suggest that BW, as indexed by genetic variants, has a causal relationship with cortical brain structure in these regions whereby higher BW is related to higher insular lobe cortical volume and surface area globally, in the insular lobe and the medial orbitofrontal and IFG parcels. All non-significant MR relationships are reported in **Appendix B3.2.4** (p49-50)**.**

Table 3.5 Significant causal relationships (*Pcorr* < .05) of birth weight on cortical structure regions of interest using Mendelian Randomisation inverse weighted regression analysis

Brain Measure	Inverse Variance Weighted				Heterogeneity		Pleiotropy		
	Effect Size	S.E	p	p_{corr}	Q	p	MR Egger Intercept	S.E	p
Cortical Volume									
Lobes									
Insula	0.346	0.116	0.003	0.009**	73.754	0.780	-0.018	0.011	0.120
Cortical Surface Area									
Global	0.281	0.108	0.009	-	86.404	0.407	-0.008	0.011	0.432
Lobes									
Insula	0.371	0.115	0.001	0.005**	85.562	0.492	-0.007	0.011	0.542
Parietal	0.224	0.109	0.041	0.068·	83.539	0.494	-0.006	0.011	0.577
Parcellations									
Medial Orbitofrontal	0.417	0.125	0.001	0.006**	91.029	0.281	-0.021	0.012	0.087
Middle Temporal	0.287	0.130	0.027	0.045*	93.387	0.227	0.001	0.012	0.916
Inferior Frontal Gyrus	0.358	0.117	0.002	0.009**	76.498	0.707	-0.006	0.011	0.594

***$p_{corr} \leq .001$, **$p_{corr} \leq .01$, *$p_{corr} \leq .05$, ·$p_{corr} \leq .10$, **S.E** = Standard Error

3.7 Discussion

In the present study we found higher BW, using the whole range, to be significantly associated with larger brain cortical volume and surface area globally (β = .104, .100 respectively) and across several localised regions of the cortex; including frontal, temporal and parietal areas (β range = .032, .040). However, higher regional cortical thickness was related to lower BW in the occipital region (β = -.064, -.110), which corroborates some previous reports (De Bie et al., 2011, Bjuland et al., 2013, Martinussen et al., 2005). Importantly, these associations were robust when covarying for age, sex, height and socioeconomic (Townsend) deprivation scores. When analysing only normal ranges of BW, fewer significant associations were found however, the same positive associations were apparent for cortical volume and surface area globally (β = .097, .088 respectively). MR analysis on significant cortical regions suggested a causal link between BW, indexed by genetic variants, and insular lobe cortical volume as well as surface area globally, in the insular lobe and in middle temporal, medial orbitofrontal and IFG parcels; whereby lower BW causes lower cortical volume or surface area in these regions.

Our results, of higher BW being associated with larger cortical volume and surface area, support several previous findings (Haukvik et al., 2014, Skranes et al., 2013, Raznahan et al., 2012, Walhovd et al., 2012, De Bie et al., 2011, Taylor et al., 2011, Martinussen et al., 2005, Allin et al., 2004). However, our sample size and analytic approach allowed us to identify several more specific, significant regions than has been previously possible, and to formally explore a causal hypothesis. Furthermore, this relationship was also present when restricting our analyses to the normal BW range, suggesting that these results were not driven by the 12.44% of the data set with abnormal (< 2.5, > 4.5kg) BW. A large number of regions in the present study appear to be implicated in the effects of BW on cortical surface area in particular, suggesting that surface area is most susceptible to prenatal disruptions independent of biological size (indexed by height); predominantly in the frontal, temporal and parietal regions. This is consistent with neonatal findings of LBW/VLBW populations (Kapellou et al., 2006). Lower surface area in these areas has also been related to lower intelligence quotient (IQ) in VLBW adults (Skranes et al., 2013) cognitive ageing in healthy older adults (Cox et al., 2017,

Walhovd et al., 2016) and in psychiatric disorders (Rimol et al., 2012). These findings are further supported by recent evidence to suggest that increasing head size does not lead to a bigger brain across all regions, rather, there is a disproportionate areal up-scaling of fronto-parietal networks which are linked with markers of heightened metabolic cost (Reardon et al., 2018) thus, one reason that individuals who are born with lower BW have lower surface area in these regions may be due to an effort to reduce this cost. Together, these results provide further evidence of the neurodevelopmental origins of both cognitive impairments (Walhovd et al., 2016) and psychiatric disorders (Weinberger, 2017, Bora, 2015, Weinberger, 1987) as well as the specific role of surface area in this theory.

The literature for associations of BW with cortical thickness has been less consistent. Some studies report lower BW to be associated with a thinner cortex in some regions but a thicker cortex in others (Bjuland et al., 2013, Raznahan et al., 2012, De Bie et al., 2011, Martinussen et al., 2005) or no effects (Haukvik et al., 2014). In the current study we found lower BW to be associated with higher lateral occipital cortical thickness, an association which has been previously reported (Martinussen et al., 2005, Sowell et al., 2008), but no evidence of a significantly thinner cortex in any region thus, partially supporting previous findings (Bjuland et al., 2013, De Bie et al., 2011, Martinussen et al., 2005).

Cortical volume is the mathematical product of surface area and thickness (Wierenga et al., 2014, Jalbrzikowski et al., 2013), thought to be under partially distinct genetic influence (Panizzon et al., 2009). As global effects in the current study were significant for cortical surface area but not thickness, volume effects in the present study appear to be driven by surface area. This pattern of relative importance of surface area but not thickness has been previously reported in relation to BW in adults (Hogstrom et al., 2013, Raznahan et al., 2012) as well as cognition in adults up to 73 years old (Cox et al., 2017); further highlighting the potential susceptibility of surface area to long-term effects of prenatal disruptions.

After conducting MR analysis on all significant cortical associations, a causal link was found between BW, as indexed by genetic variants, and surface area globally, in the insular lobe and the middle temporal, medial orbitofrontal and IFG parcels, as well as insular lobe cortical volume, which were not driven by pleiotropic effects. A nominally significant association was also found for parietal lobe surface area. Furthermore, insular cortical volume as well as surface area of frontal and temporal regions have been formerly linked with the development or duration of psychiatric disorders, such as schizophrenia and bipolar disorder, using a range of modalities (Roberts et al., 2017, Takei et al., 2013, Rimol et al., 2012, Harms et al., 2010, Wylie and Tregellas, 2010, Ha et al., 2009, Adler et al., 2005). Specifically, Harms et al. (2010) found an association between cortical volume of the IFG and an increased familial risk of schizophrenia. In relation to cognition, Colom et al. (2013) found cortical volume and surface area of frontal areas to be related to fluid and crystallised intelligence in young, healthy individuals. Thus, we have provided some evidence from MR indicating that higher BW may contribute to resilience in individuals with developmental origins of cognitive/psychiatric disorders mediated by frontal regions and, potentially, reduce cognitive impairments and the detrimental effects of psychiatric disorders. However, further testing is required to determine if these association between BW and cortical volume and surface area is found to be causal in a larger sample.

Rapoport et al. (2005b) noted that the majority of events that can adversely affect the foetus will also hinder foetal growth. Thus, despite no current evidence of a causal influence of BW on the majority of brain regions, utilising measures to identify and prevent foetal growth restriction (such as customised growth charts, using GROW software (Gestation Related Optimal Growth (Clifford et al., 2013)) *might* ensure that all foetuses reach their genetic growth potential, assuming optimal in utero environment. These types of measures could potentially help prevent or reduce the detrimental effects of lower BW, in the general population, on cortical brain development however, empirical testing of this is still required.

3.7.1 Strengths and Limitations UKB has data relating to the maternal histories for the participants in the study but not for the individual's own birth, thus there was no way to account for gestational age in the current study and it was therefore not possible to investigate specific effects of preterm birth and IUGR directly. Although gestational age may give us a more accurate picture of the foetal development in these individuals, differences in BW have been previously reported in studies testing participants who all had the same gestational age (Jablensky et al., 2005); lending credence to the current results.

The age range in the current sample was older than previously tested (45-78 years) with a cross-sectional design. Although significant effects in this study, along with results from previous cohorts (Bjuland et al., 2013, Walhovd et al., 2012, De Bie et al., 2011, Taylor et al., 2011, Martinussen et al., 2005), suggest the impact of BW on cortical morphology, particularly in relation to surface area (Walhovd et al., 2016), we cannot determine if these effects were present from early life for the current participants. Future studies of all three cortical metrics, with a longitudinal sample are required.

As part of this study, we conducted the largest BW GWAS, to date and identified the largest number of BW-associated SNPs in order to create an IV to test for causal associations. Furthermore, using an MR approach to indicate causation of the associations between BW and brain cortical structure is novel in this area however, this method has its limitations. MR assumes robust associations between the genetic variant and the outcome but, despite statistical considerations, it is difficult to completely rule out pleiotropic effects (Hemani et al., 2018) and it is thus possible that some of the variants here may not have a direct effect on brain structure. Replication of this genetic analysis in a much larger sample, with more statistical power, is desirable.

This is the first study, to our knowledge, to assess whether individual differences in BW, as a continuum, across an older (over 30 years old), mainly healthy, population-based cohort are related to three major cortical brain outcomes (cortical volume, surface area and thickness).

These considerations mean our results will have a greater relevance to the broader, non-clinical members of the population as well as an increase in statistical power as a result of not dichotomising BW. It is also the largest BW study to analyse the brain at the global, lobar and parcellated level, using a single scanner, allowing for more reliable detection of small effects (K. Miller et al., 2016a). This increase in statistical power is helpful in this area; where subtle variations in BW could be linked to small effects on brain cortical structure and, in turn, lead to increased risk of psychiatric diagnoses and cognitive difficulties.

3.7.2 Conclusion Establishing that BW variation is associated with cortical morphology in a large, middle-to-older aged, population-based sample, and when assessing normal BW ranges, gives further support to the hypothesis that subtle differences in BW may have life course effects on cortical structural development. Further, we have identified a tentative causal relationship between BW and the cortical structure of several distinct regions whereby, lower BW, indexed by genetic variants, is thought to cause lower insular cortical volume as well as global, insular, middle temporal, medial orbitofrontal and IFG surface area. Cortical structure has been previously associated with intelligence as well as an increased familial risk of schizophrenia, contributing to evidence for the neurodevelopmental origins of psychiatric disorders hypothesis. Moreover, BW has been linked with a number of prenatal insults and could potentially be a modifiable risk factor. The data therefore support the concept that optimal foetal growth (i.e. when a foetus reaches its individual growth potential) is important for brain structure in adulthood, highlighting the importance of devising better methods for detecting those at risk of sub-optimal growth in order to prevent such restrictions. These interventions could improve brain development and possibly lessen cognitive impairments as well as the cortical deficits associated with common psychiatric disorders.

3.8 Chapter Conclusion

Chapter Three thus provides evidence that lower birth weight was related to lower cortical volume and surface area over vast areas of the cortex, but higher cortical thickness in the occipital region only. Importantly, these global cortical volume and surface area effects were

also present when restricting the sample to only include individuals within the normal birth weight range, suggesting that the impact of birth weight on cortical structure can occur within subtle variations in weight within the wider population. We also provided evidence of a potential causal effect of birth weight, as indexed by genetic variants, on several measures of cortical volume and surface area. These results may therefore also partially explain the links between an increased risk of psychiatric disorders, such as schizophrenia, in individuals with lower birth weight however, schizophrenia associations were not specifically tested in this chapter. The next chapter therefore aims to use a PGRS-SCZ to further investigate the relationship between cortical structure, birth weight and schizophrenia.

Chapter Four

Impact of polygenic risk for Schizophrenia on cortical structure in UK Biobank

4.1 Background

As noted in Chapter Two, a negative association was found between PGRS-SCZ and global cortical thickness. This relationship suggests that having a higher genetic loading for schizophrenia is related to lower cortical thickness across the entire brain. This effect was found across the whole sample and therefore, not limited to those who developed schizophrenia. Furthermore, the sample size was too small to rely firmly on these conclusions and measures of cortical volume and surface area were not assessed. The aim of Chapter Four was therefore to determine if this result can be replicated in a larger population-based sample – UKB, as well as to determine if any links exist between PGRS-SCZ and cortical volume and/or surface area. In addition, as birth weight (a proxy for obstetric complications) is a known risk factor for schizophrenia (Lærum et al., 2017, Rubio-Abadal et al., 2015, Forsyth et al., 2013, Clarke et al., 2006, Jablensky et al., 2005, Cannon et al., 2002b, Geddes and Lawrie, 1995) and was previously associated with cortical structure in Chapter Three, we also considered a potential relationship between this and both PGRS-SCZ and a birth weight × PGRS-SCZ interaction on cortical structure, in an attempt to address potential gene × environment interactions.

This chapter is presented as the manuscript that is under review at *Biological Psychiatry* in which, I am the first author. I can also confirm that I was responsible for the design of the experiment, analysing the data and writing the paper for this submission.

4.2 Paper: Impact of polygenic risk for Schizophrenia on cortical structure in UK Biobank

4.3 Abstract

Background: Schizophrenia is a highly heritable, neurodevelopmental disorder with many genetic variants of individually small effect contributing to phenotypic variation. Generally lower cortical thickness (CT), surface area (SA) and cortical volume (CV) have been demonstrated in schizophrenia . Furthermore, a range of obstetric complications (e.g. lower birth weight) are consistently associated with an increased risk for schizophrenia. We investigated whether a high polygenic risk score for schizophrenia (PGRS-SCZ) is associated with CT, SA and CV in a large population-based sample, and tested for interactions with birth weight.

Methods: Structural 3T MRI scans, acquired on a single scanner, and genetic data were available for 2,864 UK Biobank (UKB) participants (n_{male}/n_{female} = 1382/1482; mean age at time of scan = 62.35 years, ± S.D = 7.40). Linear mixed models were first used to test for associations between PGRS-SCZ and global and localised regions of CV, SA and CT. Secondly, linear regression was used to check for potential associations between PGRS-SCZ and birth weight, followed by linear mixed models to test for interaction effects of these variables on cortical structure. Results are reported using SNP inclusion threshold of $P \leq 0.1$ and false discovery rate correction of $P < 0.05$.

Results: We found a significant negative effect of PGRS-SCZ on global CV (β = -.033, p = .039, p_{corr} = .195) and CT (β = -.043, p = .012, p_{corr} = .020), in that a higher PGRS-SCZ was associated with lower volume and thickness across the whole brain. We also report a significant negative association in insular lobe CT (β = -.050, p_{corr} = .025). No significant effects were found for SA. Furthermore, PGRS-SCZ was not associated with birth weight and no PGRS-SCZ × birth weight interactions were found for these cortical regions.

Conclusions: These results suggest that individual differences in CT are partly influenced by genetics and are most likely not due to factors downstream of disease onset. This approach may help to elucidate the genetic pathophysiology of schizophrenia. Further investigation in case-control and high-risk samples could help identify any localised effects of PGRS-SCZ as symptoms develop. Future studies should also further investigate other potential environmental effects on CT.

4.4 Introduction

Schizophrenia is a heterogeneous psychiatric disorder with twin heritability estimates (h^2) of ~80% (Matheson et al., 2011, Gejman et al., 2010, Purcell et al., 2009). Recent evidence suggests that the disorder is polygenic in nature, (Lee et al., 2012, Matheson et al., 2011, Gejman et al., 2010, Purcell et al., 2009) with genome-wide association studies (GWAS) identifying specific schizophrenia-inferring loci (SWG-PGC, 2014, CDG-PGC, 2013, Purcell et al., 2009). In line with a neurodevelopmental theory of schizophrenia, cortical deficits have been consistently associated with the disorder which are thought to predate disorder onset (Kinros et al., 2010, Rapoport et al., 2005a) and are caused by a combination of genetic and environmental factors (Rapoport et al., 2005b, Kinros et al., 2010). Limited research has fully explored the links between polygenic risk for schizophrenia and cortical structure with consideration of other schizophrenia risk factors.

Differences in some aspects of brain structure have been consistently detected in groups of patients with schizophrenia compared to healthy controls (Kong et al., 2015). Recently, the field has moved towards studying cortical volume (CV), thickness (CT) and surface area (SA). These metrics are considered to have distinct developmental trajectories (Wierenga et al., 2014) and a lot of evidence suggests that variation in these traits are heritable; h^2 ranges from 66-97% for CV (Peper et al., 2007) and averages around 80% for global CV (Kremen et al., 2010, Wright et al., 2002), 81% for CT (Panizzon et al., 2009) and 89% for SA (Panizzon et al., 2009).

CV has been most studied in schizophrenia, reporting lower CV in widespread areas of the brain in patients (Gupta et al., 2015, Kong et al., 2015, Rimol et al., 2012, Olabi et al., 2011, Ellison-Wright and Bullmore, 2010, Gutiérrez-Galve et al., 2010, Goldman et al., 2008, Honea et al., 2008, Goghari et al., 2007, Honea et al., 2005) and in the healthy relatives of individuals with schizophrenia as compared to controls (Brans et al., 2008, Boos et al., 2007, Goghari et al., 2007, Cannon et al., 2002b). However, as CV is the product of CT and SA (Wierenga et al., 2014, Jalbrzikowski et al., 2013, Panizzon et al., 2009) studying volume alone may obscure

some associations between schizophrenia and brain structure (Kong et al., 2015, Panizzon et al., 2009). Lower CT has been associated with schizophrenia in several brain regions (Kong et al., 2015, Hartberg et al., 2011, van Haren et al., 2011, Rimol et al., 2010, Goldman et al., 2009, Fornito et al., 2008, Kuperberg et al., 2003) and widespread patterns across the cortex (Kong et al., 2015, Sprooten et al., 2013, Crespo-Facorro et al., 2011, Rimol et al., 2010, Yang et al., 2010, Nesvåg et al., 2008, Goghari et al., 2007, Narr et al., 2005). Further, CT differences have been evidenced in frontal and temporal lobes of individuals at familial high-risk of schizophrenia when compared to controls (Bois et al., 2015b, Sprooten et al., 2013, Byun et al., 2012, Ziermans et al., 2012, Jung et al., 2011, Goghari et al., 2007) and thus may be more easily identified in those at a higher genetic risk of the disorder. SA schizophrenia associations have received less empirical attention and existing studies report inconsistent findings (Gutiérrez-Galve et al., 2010). Whilst some studies suggest cortical SA is lower in schizophrenia patients compared to controls both globally (Palaniyappan et al., 2011) and in specific regions (Rimol et al., 2012, Hartberg et al., 2011, Palaniyappan et al., 2011, Gutiérrez-Galve et al., 2010), whereas others have found SA to be higher (Bois et al., 2015a, Fornito et al., 2008) or no different (Hedman et al., 2016, Crespo-Facorro et al., 2011) in these groups.

Recently, large GWASs have been used to identify genetic variants associated with schizophrenia (SWG-PGC, 2014, Lee et al., 2012, Purcell et al., 2009). From these findings, a polygenic risk score for schizophrenia (PGRS-SCZ) has been calculated (SWG-PGC, 2014, CDG-PGC, 2013, Ripke et al., 2013, Purcell et al., 2009); a higher score relating to a greater risk of developing the disorder. PGRS-SCZ allows for the assessment of genetic liability in the population – even among people who never develop the illness - and enables use of large-scale samples such as UK Biobank (UKB; http://www.ukbiobank.ac.uk/).

A small number of studies have tested PGRS-SCZ in relation to structural brain imaging phenotypes with inconsistent results. Reus et al. (2017) found no associations between regional subcortical volume or white matter microstructure and PGRS-SCZ using a subset of the same sample and same imaging protocol as the current study (n = 978) but did not assess

any cortical metrics. Some studies have reported higher PGRS-SCZ to be associated with a decrease in global grey and/or white matter volume (Caseras et al., 2015, Oertel-Knöchel et al., 2015, Terwisscha van Scheltinga et al., 2013) ($n_{individuals}$ range = 89-274) with relatively small effect sizes and amount of variance explained (β = - .151, ΔR^2 = .023 (change in R^2 for regional white matter volume when PGRS-SCZ is added to hierarchical regression analyses), R^2 = .042 (total brain volume); whilst others did not find an effect (van der Auwera et al., 2015, Papiol et al., 2014). Higher genetic loading for schizophrenia has also been previously associated with lower global CT in a case-control sample, regardless of group, as well as lower temporal CT in patients but not controls (Neilson et al., 2017a, Chapter Two). Lancaster *et al.* (2018) found no such association in a healthy control sample but did report nominal regional CT effects. Due to the limited sample sizes (*n* range = 75-99), replication of these findings is required.

Another important consideration, as per neurodevelopmental theories of the disorder (Kinros et al., 2010, Rapoport et al., 2005a, Rapoport et al., 2005b), relates to potential effects of other risk factors for schizophrenia and their interactions between schizophrenia liability and cortical structure. Several obstetric complications (OCs), for example, have been consistently identified as risk factors for schizophrenia with some, such as birth weight, considered to be influenced by both genetic and environmental components (Gielen et al., 2008). Previous studies have also suggested that OCs are associated with greater cortical structure deficits in schizophrenia patients compared to controls (Cannon et al., 2002, van Erp et al 2002b). All three of the currently studied cortical metrics are considered to be highly susceptible to both genetic and environmental insults (Lyall et al., 2015). with subtle differences in birth weight, in particular, previously linked to lower CV, SA (Haukvik et al., 2014, Raznahan et al., 2012, Walhovd et al., 2012,) and CT (Raznahan et al., 2012) later in life. Mendelian Randomisation analysis of birth weight-associated single nucleotide polymorphisms (SNPs) also suggest that, for global and some localised regions of SA and CV, this effect may be causal (Chapter Three). Moreover, evidence suggests that a genetic liability for schizophrenia can lead to higher susceptibility for experiencing OCs (Li et al., 2016, Walder et al., 2014) and that these

complications could themselves be associated with the schizophrenia-associated genes (Forsyth et al., 2013). Given this and the aforementioned associations between birth weight and schizophrenia, we also tested here whether the PGRS-SCZ was associated with birth weight and if any interactions were present between the two in relation to cortical structure.

The current study therefore aims to examine the relationship between PGRS-SCZ and cortical structure in a population-based sample collected on a single scanner. Global and regional CV, CT and SA measures were analysed, with the specific hypothesis that PGRS-SCZ would be associated with lower global CT. Lower global, frontal and temporal CT in particular has been found in those at familial high-risk and global CT has been previously associated with a higher PGRS-SCZ. Furthermore, we predicted that these effects would interact with birth weight; individuals with a higher PGRS-SCZ and lower BW would have smaller CV, CT and SA.

4.5 Methods

4.5.1 Participants Detailed participant information has been reported previously (Cox et al., 2016) (http://www.ukbiobank.ac.uk/participants/) and in **Appendix C4.1.1** (p65). The current study included individuals with complete genetic and cortical data for three cortical parameters (CT, SA and CV). Birth weight information was also recorded for these individuals, along with whether they were part of a multiple birth. Participants were excluded based upon overlap in Psychiatric Genomics Consortium (PGC) training samples and schizophrenia status, see ***Derivation of Polygenic Risk Scores*** and **Appendix C, Fig C4.1** (p66) for further information. Furthermore, global cortical outliers (±3 S.D.s), were removed for all three cortical parameters, resulting in a current sample of 2,864 individuals ($n_{males}/n_{females}$ = 1382/1482; mean age at time of scan = 62.35 years, S.D = ±7.40 years, range = 46-78 years). Ethical approval for UKB was received from the research ethics committee (REC reference 11/NW/0382) under application 4844. Informed consent was provided by all participants (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200).

4.5.2 Imaging Procedures UKB imaging details in full are described elsewhere (Alfaro-Almagro et al., 2017, K. Miller et al., 2016, Cox et al., 2016) (https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). In summary, images were acquired on a single Siemens Skyra scanner. Structural brain images were acquired in the sagittal plane using a T1-weighted, three-dimensional, magnetization-prepared rapid gradient-echo sequence at a resolution of 1x1x1mm with a field of view of 208x256x256. Further information on the imaging protocol (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367) and imaging acquisition parameters (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977) are documented online. Brain scans were anonymised at the time of acquisition and were processed locally on a server cluster at Centre for Cognitive Ageing and Cognitive Epidemiology (CCACE, http://www.ccace.ed.ac.uk/), in Edinburgh using FreeSurfer (v5.3, http://surfer.nmr.mgh.harvard.edu/).

4.5.3 MRI Analysis We processed the T1-W volumes from the first UKB imaging release locally to derive cortical measures of thickness (mm), surface area (mm^2) and volume (mm^3), for further details see **Appendix C4.1.2** (p66-68)**.** Briefly, parcellation of cortical structures was conducted in FreeSurfer v5.3 using the Desikan-Killiany neuroanatomical atlas (Desikan et al., 2006). This generated 34 bilateral cortical parcels that can be attributed to eight lobar structures, each with volume, surface area and mean thickness measures (Desikan et al., 2006). Eleven parcels were combined into four larger regions as previously described (Cox et al., 2017, Klein and Tourville, 2012); resulting in 27 bilateral regions of interest (ROIs) which were assigned to one of eight lobar regions, see **Appendix C4.1.2** (p66-68)**.** The X, Y and Z co-ordinates of the centre of the brain mask within the scanner (http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25756, http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25757, http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25758) were also fitted as covariates for the current analyses to account for varying head positions in the scanner; see **Appendix C4.1.5** (p69) for further information on these variables.

4.5.4 MRI Quality Control Procedures Quality checks were conducted on the success of processing on all scans. T1-weighted images were initially carried out by UKB (Brain Imaging Documentation V1.1, http://www.ukbiobank.ac.uk, Alfaro-Almagro et al., 2018) with further Quality Control (QC) procedures carried out locally. For local QC procedures (see Cox et al., 2017) and http://enigma.ini.usc.edu/protocols/imaging-protocols/), images were visually assessed for major errors (e.g. zero or partial output, substantial skull strip issues or tissue identification issues) which removed 458 scans, see **Appendix C, Fig. C4.1** (p66). The remaining 3,875 scans were then assessed for minor errors (e.g. erroneous boundary placement, minor skull stripping issues and minor tissue omission) which resulted in removal of individual regions within scans (6,192 of the possible 295,052 regions were removed). As global information was largely unaffected by the FreeSurfer reconstruction process, global and lobar values were extracted from the data with major errors removed but did not undergo QC exclusion for minor errors. However, exclusion of global cortical outliers (±3 S.D.s) provided a further internal imaging QC as in previous publications (Reus et al., 2017, Shen et al., 2017).

4.5.5 Genotyping and Imputation Processing Procedures for genotyping, imputation and quality control for UKB have been reported previously (Howard et al., 2018, Luciano et al., 2018, Bycroft et al., 2017, Wain et al., 2015). Briefly, 488,377 blood samples were assayed using two different genotyping arrays; Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (Wain et al., 2015) and Applied Biosystems UKB Axiom Array (http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UK-Biobank-Axiom-Array-Content-Summary-2014.pdf). Further information on these arrays can be found in **Appendix C4.1.3** (p68-69).

Genetic QC was performed using the approach described by Howard et al. (2018). Firstly, participants were excluded based on shared genetic relatedness, up to the third degree, using kinship coefficients (>.044) identified using the KING toolset (Manichaikul et al., 2010) as previous (Howard et al., 2018, Bycroft et al., 2017). To maximise the sample, we subsequently added back in one member from each group of related individuals, using a genomic relationship matrix, and selected only those with a relatedness of less than .025 with any other

individual. Individuals were also excluded based upon a combination of both self-reported ethnicity and a principal component (PC) analysis (see **Appendix C,** p66 and 69) which revealed individuals with similar ancestral backgrounds. The final QC exclusion criteria included variant missing-ness per individual (>2%), gender mismatch, or a self-declared, non-white British ancestry, variant call rate (<98%), Hardy-Weinberg equilibrium ($P < 10^{-6}$), minor allele frequency < .01, an imputation quality < .1, resulting in 331,374 individuals and 7,730,951 variants.

4.5.6 Derivation of Polygenic Risk Score PGRS-SCZ were constructed using PLINK v1.9 (Purcell et al., 2007) to calculate the sum of all alleles that are associated with schizophrenia, across many genetic loci, and weighting these alleles by their effect sizes. These effect sizes have been previously estimated in the most recent PGC schizophrenia (PGC-SCZ, https://www.med.unc.edu/pgc/pgc-workgroups) GWAS (36, 989 cases vs 113,075 controls; SWG-PGC, 2014). Individual identifiers were not available for PGC-SCZ within this sample thus, in an attempt to reduce the likelihood of any potential overlap between PGC-SCZ and the current sample, individuals form the PGC Major Depressive Disorder working group training sample (Wray et al., 2018) were excluded (n = 92). For the same reason, UKB individuals who reported a diagnosis of schizophrenia were also excluded (n = 812, see **Appendix C, Fig. C4.1,** p66) Schizophrenia status was determined from two separate variables within UKB: International Classification of Diseases (ICD-10) diagnosis (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=41202; F20-F29 Schizophrenia, schizotypal and delusional disorders) and non-cancer illness (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20002). The former is a summary of the distinct diagnoses given from episodes in hospital; the latter was coded by a trained nurse, based on the description of a non-cancer illness given by the participant.

To create a SNP-set in approximate linkage equilibrium, clump-based linkage disequilibrium (LD) pruning was performed with a r^2 of < 0.25 within a 200kb window. For the remaining SNPs, marker weights (logarithm of the Odds Ratio) and p-value association statistics for individual SNPs were derived from the most recent PGC GWAS of schizophrenia (9.8 million

autosomal SNPs) (SWG-PGC, 2014). Five scores were generated for each individual, using SNPs selected according to the significance of their association with the phenotype in the discovery GWAS at nominal P-value thresholds of 0.01, 0.05, 0.1, 05, 1, as previously described (Purcell et al., 2009). The SNP inclusion threshold was set at $P \leq 0.1$ for the main results in this paper, as this threshold was shown to explain the most phenotypic variance in the discovery cohort (SWG-PGC, 2014). There were 86,124 SNPs, available in the current sample after QC, using the $P \leq 0.1$ threshold. For results produced using the remaining SNP inclusion thresholds ($P \leq 0.01$, 0.05, 0.5 and 1) see **Appendix C4.2.2** (p72-83). PCs were also calculated to account for population stratification, further information of this process can be found in **Appendix C4.1.5** (p69). The first 15 PCs were used in the current analysis.

4.5.7 Measure of Birth Weight Participants were asked to provide their own birth weight information in UKB. Recalled birth weight has been shown to have high agreement with recorded birth weight and considered a valid and suitable measure for epidemiological studies (Shenkin et al., 2017). Birth weight data were collected at initial assessment and at the first repeat assessment (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20022). As information from both instances were comparable (r = .94), the birth weight variable included data from instance one as default, NA values from instance one were replaced by data from instance two. The birth weight range in the current sample was .91-5.78kg (mean = 3.40kg, S.D = ±.61kg). Furthermore, only individuals who reported to not be part of a multiple birth were included (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1777).

4.5.8 Covariates *Socioeconomic Deprivation* was measured using the Townsend deprivation index (range = -6.26 – 9.16, mean = -1.98, S.D = ±2.68), calculated when the participant joined the UKB study. Individuals were assigned a score based on census output regarding their postcode (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=189). *Standing height* was measured using a Seca 202 device (range = 143 – 196cm, mean = 169.74cm, S.D = ±9.20cm) and was collected at initial assessment, first repeat assessment and at time of scan (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=50), data from both instances were

comparable (r = .99). As with birth weight, data from the first instance was used by default and missing values from instance one were replaced by data from instance two.

4.5.9 Statistical Analysis All analyses were conducted in R (v3.2.3).

4.5.9.1 Associations Between PGRS-SCZ and Cortical Structure Linear mixed effects (LME) models (package "nlme", v3.1-127, Pinheiro et al., 2017) were used to determine whether PGRS-SCZ (independent variable) were associated with cortical structures (dependent variable). LME models were first conducted in a repeated measures format with hemisphere fitted as a random factor. Analyses were also conducted to determine if there was a PGRS-SCZ × hemisphere interaction which would require testing as an independent measure. This model included age, age^2, sex, genotype array, 15 PCs and X, Y and Z co-ordinates of the brain mask within the scanner. ICV was also included as a fixed effect for lobar and parcellation analyses to control for the size of specific regions relative to the whole brain. This measure of ICV was derived based on a UKB IDP similar to that calculated by Statistical Parametric Mapping methods (https://www.fil.ion.ucl.ac.uk/spm/) whereby grey matter, white matter and ventricular cerebral spinal fluid are added together. Here we only report statistically significant associations (P < .05) between PGRS-SCZ and cortical brain structure from these models. Furthermore, the reported results were analysed using the SNP inclusion threshold of $P \leq 0.1$ as this threshold explained the most phenotypic variation in the discovery cohort (SWG-PGC, 2014). Non-significant associations as well as results for all other thresholds as can be found in **Appendix C4.2** (p72-83)**.** Standard regression coefficients are reported throughout. Utilising the 'p.adjust' function in R ('stats' package v3.2.3), the false discovery rate (FDR) method, with a rate of P < .05 (Genovese et al., 2002), was used to correct results for multiple comparisons.

4.5.9.2 Associations Between PGRS-SCZ and Birth Weight Using the full sample of individuals with cortical, BW and genotype information, excluding global cortical outliers (n = 1,659, $n_{males}/n_{females}$ = 696/963; mean age at time of scan = 60.79 years, S.D = ±7.41 years, range = 46-78 years), a generalised linear model regression (package "glm2", v1.1.3) was

used, to test for associations between PGRS-SCZ (independent variable) and birth weight (dependent variable). This model included all fixed effects outlined in ***Associations between PGRS-SCZ and cortical structure,*** with the addition of height and socioeconomic deprivation as in previous publications (Haukvik et al., 2014, Raznahan et al., 2012), as fixed effects. LME models, using these same fixed effects with the addition of a PGRS-SCZ × BW interaction, along with main effects terms, were also used to test for potential interactional effects on cortical structure.

4.6 Results

4.6.1 Demographics Statistical analyses were conducted to determine if any of the current demographic variables were associated with PGRS-SCZ at the $P \leq 0.1$ threshold (see **Table 4.1**). No significant associations were found ($P > 0.05$).

Table 4.1 Descriptive statistics for demographic variables and their associations with PGRS-SCZ

	Range	Mean	S.D	Statistics
Gender ($n_{males}/n_{females}$=1382/1482)	-	-	-	$X^2 = 2707.8$, $p = .513$
Age	46, 78	62.35	7.40	$r = -.003$, $p = .863$
Birth weight (kg)	.91, 5.78	3.40	.61	$r = -.044$, $p = .069$ **.**
Height (cm)	143, 196	169.73	9.12	$r = -.033$, $p = .077$ **.**
Townsend Deprivation Scale	-6.26, 9.16	-1.98	2.68	$r = .017$, $p = .363$

***$p_{corr} \leq .001$, **$p_{corr} \leq .01$, *$p_{corr} \leq .05$, **.** $p_{corr} \leq .10$, **S.D** = Standard deviations
Mean, S.D. and range of all demographic variables within the current sample as well as test statistics for associations with PGRS-SCZ at the $P \leq 0.1$ threshold (n = 2.864)

4.6.2 Associations Between PGRS-SCZ and Cortical Structure Results for PGRS-SCZ × hemisphere interactions on cortical structure can be found in the **Appendix C4.2.1** (p69-72). No significant hemisphere interactions were found in the current study, at the $P \leq 0.1$ threshold, thus all analyses were conducted utilising the aforementioned repeated measure design.

A significant negative effect of PGRS-SCZ on global CV (β = -.033, p = .039, R^2 = .001, **see Fig. 4.1a**) and CT (β = -.043, p = .012, R^2 = .002, **see Fig. 4.1b**) was found, in that a higher PGRS-SCZ was associated with lower CV and CT across the whole brain. However, only the association with CT remained significant after multiple correction across all three cortical metrics(CT p_{corr} = .020, CV p_{corr} = .195).

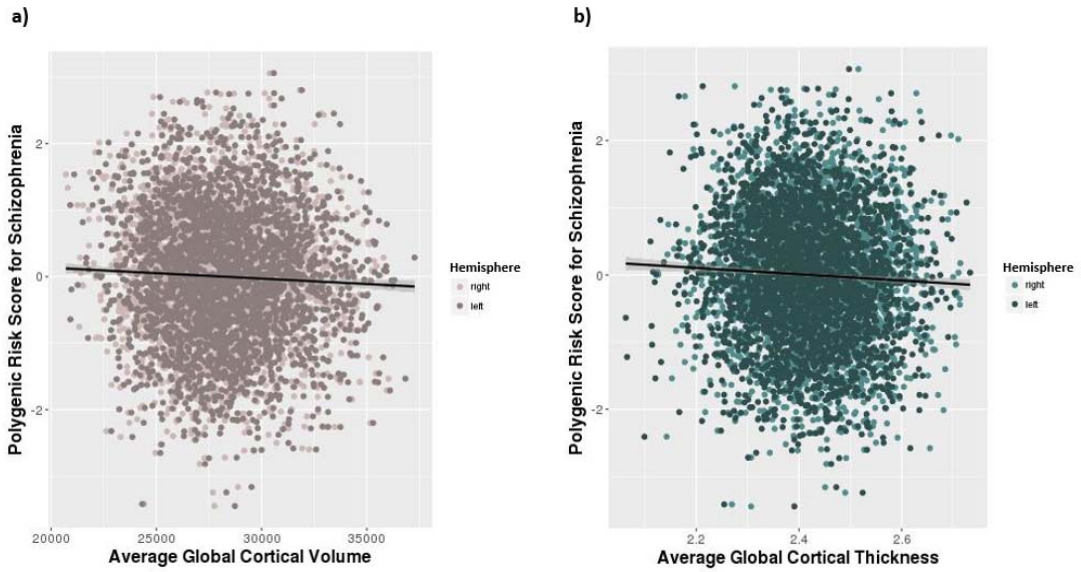

Fig. 4.1 Scatter plots showing a higher PGRS-SCZ is associated with a) lower global cortical volume (mm^3) and b) lower global cortical thickness (mm) in the left and right hemisphere (n = 2,864)

PGRS-SCZ was also negatively associated with insular lobe CT (β = -.050, p_{corr} = .025, R^2 = .002, **see Fig. 4.2**). No associations between PGRS-SCZ and SA were found at any threshold; this was true for all global, lobar and parcellation measures, see **Appendix C4.1** (p72-82)**.**

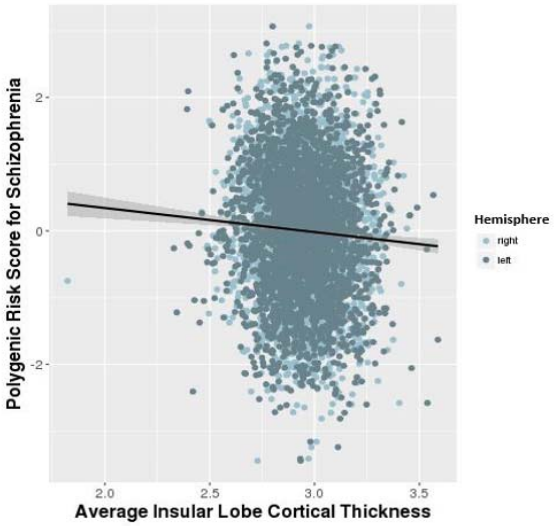

Fig. 4.2 Scatter plots showing a higher PGRS-SCZ is associated with lower insular lobe cortical thickness (mm) in the left and right hemisphere (*n* = 2,864)

4.6.3 Associations Between PGRS-SCZ and Birth Weight There was no association between PGRS-SCZ, at any threshold, and birth weight. This was true for both the base and fully-adjusted model. (**See Table 4.2**)

Table 4.2 Results for associations between PGRS-SCZ and birth weight at all *P* thresholds (*n* = 1,659)

PGRS Threshold	*Fully Adjusted Model*			
	Effect Size	S.D	p value	p_{corr}
***P* ≤ 0.01**	-0.016	0.024	0.513	0.513
***P* ≤ 0.05**	-0.037	0.024	0.122	0.305
***P* ≤ 0.1**	-0.041	0.024	0.090	0.305
***P* ≤ 0.5**	-0.021	0.024	0.380	0.513
***P* ≤ 1**	-0.019	0.024	0.423	0.513

S.D = Standard deviation

4.6.4 Effects of Interactions Between Birth Weight and PGRS-SCZ on Cortical Structure

No significant interactions between birth weight and PGRS-SCZ impacting upon global CV or CT were found. See **Table C4.5** in **Appendix C4.2.3** (p83-96) for full results**.**

4.7 Discussion

This is one of the first studies to analyse associations for CV, CT and SA measures within a single large, population-based sample, and the first to our knowledge to examine the association between these parameters and PGRS-SCZ. We report a link between an increased genetic liability for developing schizophrenia and lower global CV and CT, as well as insular lobe CT. In this and our previous studies (Neilson et al., 2017a (Chapter Two); Neilson et al., 2017b) we primarily test and report corrected results at $P \leq 0.1$ level. We also include results corrected over all three cortical metrics to illustrate the effects of more stringent control for multiple comparisons and note that the association between PGRS-SCZ and global CV was not significant after this correction. Overall, these results suggest that lower CT, commonly reported in schizophrenia patients, may be driven by a genetic liability for schizophrenia and are most likely not due to factors downstream of disease onset (e.g. antipsychotic medication use; Lawrie et al., 2001) No significant associations were found for SA.

Previous study of associations between PGRS-SCZ and brain volume have been inconsistent. Lee et al. (2016) found ICV to be significantly linked with enrichment of schizophrenia-associated genetic variants but could not determine the direction of these effects. Another study, utilising a PGRS-SCZ created from the first PGC-SCZ GWAS (SPGWASC, 2011), found an association between decreased total brain volume and higher PGRS-SCZ (Terwisscha van Scheltinga et al., 2013) but attempts to replicate these results with the most recent PGC-SCZ GWAS findings (SWG-PGC, 2014) were unsuccessful (van der Auwera et al., 2015, Papiol et al., 2014). However, the sample sizes used within these studies are relatively small (*n* range = 122 - 763). This is especially pertinent when considering that, despite the current sample being much larger (*n* = 2,864) than these previous studies, our CV result did not survive FDR corrections for multiple comparisons over all five *P*-value thresholds. Thus, further testing in an even larger population-based samples is desirable. Calculations of the ideal sample sizes for these analyses can be found in **Appendix D** (p97-99).

The global CT association is consistent with previous familial high-risk studies for schizophrenia, which also found cortical thinning in widespread areas of the cortex both longitudinally (Hedman et al., 2016, Bois et al., 2015b, Ziermans et al., 2012) and cross-sectionally (Sprooten et al., 2013, Byun et al., 2012, Jung et al., 2011, Goghari et al., 2007). A genetic enrichment study also found several CT parcels to be associated with schizophrenia risk variants (Lee et al., 2016). Furthermore, a case-control study found that a higher PGRS-SCZ was associated with lower global CT in both the schizophrenia patient only analysis and in the whole sample (Neilson et al., 2017a, Chapter Two). Specific links between reduced insular cortex thickness and genetic risk for schizophrenia have been less commonly reported, although reductions in this region, among others, have been found in schizophrenia patients compared to controls and individuals at genetic high-risk of the disorder (Byun et al., 2012). Additionally, the insula is a region commonly reported to be involved in schizophrenia, for example in relation to auditory hallucinations (Wylie and Tregellas, 2010).

The fact that no PGRS-SCZ associations were found for surface area is not entirely surprising. Evidence of SA abnormalities associated with schizophrenia has been inconsistent (Gutiérrez-Galve et al., 2010) and familial high-risk studies have described it as a 'weak intermediate phenotype' for schizophrenia (Honea et al., 2008). However, evidence does suggest that this phenotype is highly heritable (Panizzon et al., 2009) and is associated with some deficits in the healthy relatives of schizophrenia patients (Goghari et al., 2007). A general limitation of PGRS, at present, is that the amount of phenotypic variation that they explain is far smaller than the heritability of the phenotype (Reus et al., 2017, Plomin, 2013); thus, it may be that the predictive power of PGRS-SCZ in combination with the current sample size are not large enough to detect SA effects.

No association was found between PGRS-SCZ and birth weight, nor were there interaction effects between these two factors within global CV or CT. As previous studies have found lower birth weight to be associated with lower CV (Haukvik et al., 2014, Raznahan et al., 2012, Walhovd et al., 2012), thinning and thickening across the cortex (Martinussen et al., 2005,

Raznahan et al., 2012), an increased risk of schizophrenia (Lærum et al., 2017, Cannon et al., 2002a, Geddes and Lawrie, 1995) and several independent SNPs (Horikoshi et al., 2016, Horikoshi et al., 2013); we expected to find a link between these factors. However, the current findings do not support a significant shared effect of genetic variants for schizophrenia and birth weight CT. Further investigation is needed to determine this.

4.7.1 Strengths and Limitations The main limitation of the current study and PGR-SCZ studies in general is that, at present, the variance explained by PGRS is relatively small (~2-3%; Purcell et al., 2009) and that larger sample sizes significantly increase the power of PGRS (Dudbridge, 2013). Despite this study being the largest ***imaging*** PGRS study to date, with 2,864 individuals (van der Auwera et al., 2015, Papiol et al., 2014, Terwisscha van Scheltinga et al., 2013, Reus et al., 2017), it is still relatively small compared to other PGRS studies (e.g. Liuhanen et al., 2017, Reginsson et al., 2017, Taylor et al., 2016). Furthermore, a post-hoc analysis (see **Appendix D**, p97-99) suggests that the current study was underpowered (5-41%) for some analyses, highlighting the need for even larger imaging samples. Current calculations suggest a sample of at least ~21,500 to reliably detect some effect of current PGRS-SCZ on cortical structure. Given UKB's goal of acquiring 100,000 scans by 2022 (https://imaging.ukbiobank.ac.uk/), we should be able to improve our sample size in the near future. This sample size, coupled with larger discovery GWAS, will allow for detection of smaller effects (Reus et al., 2017, Dima and Breen, 2015, Thompson et al., 2014) and may eventually allow PGRS to be used in the development of personalised medicine (Dima and Breen, 2015) however, further research would be necessary.

A further limitation, related to the derivation of the PGRS-SCZ, is that we were unable to remove any individuals utilised in the discovery dataset for the PGC schizophrenia working group that may also be included in the current UKB sample, as this information is not currently available. However, due to the methodological efforts made to overcome this issue (e.g. exclusion of schizophrenia cases and IDs from PGC MDD group) we believe this limitation to be relatively minor as effects will be restricted to healthy controls only.

Although multi-centre collaborations have made larger samples more achievable, different acquisition protocols could lead to variability in image contrast and, in turn, disagreement over brain segmentation between sites; necessitating the development of reliable acquisition protocols to attempt to reduce such issues (Schnack et al., 2010). A strength of the current study is that all brain images were collected on a single scanner using the same protocol and analysis pipeline thus, by-passing multi-scanner variability problems and the need to assess reliability. Furthermore, as UKB is a population-based sample and all schizophrenia cases were excluded, we are also able to test for associations whilst avoiding confounds such as secondary effects of illness or antipsychotic medication use (Lawrie et al., 2001).

Previous studies have reported both that individuals at familial high-risk, who developed schizophrenia, have significantly higher PGRS-SCZ than those at high-risk who remained well and that these PGRS are positively associated with gyral folding (Neilson et al., 2017b). It is possible that there are different genetic associations for different brain measures than derived for in the current study. Given the current sample consisted of older individuals (46-78 years, mean = 62.3), as compared to most schizophrenia studies (Liu et al., 2016, Caseras et al., 2015, van der Auwera et al., 2015, Papiol et al., 2014, Terwisscha van Scheltinga et al., 2013), which commonly include age ranges of 18-55 years that more closely map to age of disorder onset, we cannot rule out effects of ageing on the current results. Further investigation in prospective case-control samples is required.

Although the inclusion of birth weight, a proxy for OCs and risk factor for schizophrenia (Lærum et al., 2017, Lyall et al., 2015, Cannon et al., 2002a, Geddes and Lawrie, 1995) with both genetic and environmental components (Gielen et al., 2008), is a strength of the current paper, we cannot entirely rule out environmental effects on the results we report. For example, both cannabis use and developmental trauma have been linked with reductions in CT (Habets et al., 2011) and an accumulation of environmental risk factors (including migration, cannabis use, urbanicity, OCs and adverse events) has been associated with lower temporal CT (Neilson et al., 2017a, Chapter Two). Furthermore, cannabis use has been found to moderate

the link between PGRS-SCZ and cortical maturation (French et al., 2015). Thus, other environmental risk factors should be explored in further studies of potential gene-environment interactions on structural brain measures in schizophrenia.

4.7.2 Conclusion In summary, the current finding that lower global and insular lobe CT, is associated with an increased genetic loading for schizophrenia. This provides further evidence that individual differences in CT are, at least partly, influenced by a genetic component. Importantly, these findings also suggest that the schizophrenia and CT associations, reported here and in previous literature, are most likely not confounded by factors downstream of disorder onset (e.g. use of antipsychotic medication). Furthermore, it suggests that using a PGRS approach may help to elucidate the genetic pathophysiology of the disorder as GWAS and genomic imaging studies get larger they could identify how more specific genetic, expression and pathway effects impact upon global and/or particular brain structures, connections and networks. Further consideration of environmental risk factors for schizophrenia will also be crucial to understanding the nature of the relationship between schizophrenia and disrupted cortical structure.

4.8 Chapter Conclusion

In the current chapter, we replicated the finding of a relationship between PGRS-SCZ and global cortical thickness reported in Chapter Two. A higher PGRS-SCZ was linked with lower cortical thickness, but in a population-based sample of 2,864 individuals. Additionally, we found insular cortical thickness to present the same relationship. Furthermore, we did not find PGRS-SCZ to be associated with birth weight nor, did we find any PGRS-SCZ × birth weight interactions on cortical structure. Together these results provide further evidence of differential impacts of genetic and environmental risk factors for schizophrenia on cortical structure.

Despite this study being the largest *imaging* PGRS sample, that we are aware of, it is still relatively small for a PGRS study (e.g. Liuhanen et al., 2017, Reginsson et al., 2017, Taylor et al., 2016) and a larger sample size coupled with larger discovery GWAS may eventually allow

PGRS to be used in the development of personalised medicine (Dima and Breen, 2015). Furthermore, as in Chapter Two, other environmental risk factors should be explored in future studies of potential G × E interactions on structural brain measures in schizophrenia.

Chapter Five

General Discussion

5.1 Summary

This thesis presented, three empirical studies which investigated the potential impact of polygenic loading and environmental risk factors for schizophrenia on cortical structure. Each chapter utilised a different methodological approach in order to answer a number of important questions; (1) is a PolyGenic Risk Score for Schizophrenia (PGRS-SCZ) and/or experiencing an accumulation of environmental risk factors for schizophrenia, associated with cortical thickness (CT) (Chapter Two); (2) is birth weight associated with not only CT but also cortical volume (CV) and surface area (SA) (Chapter Three); (3) are PGRS-SCZ associated with all three cortical metrics and, if so, are these effects associated with an interaction with birth weight (Chapter Four). Ultimately, the use of a range of methodological techniques within this thesis have enabled us to determine if any associations exist between brain structure and genetic and/or environmental risk factors for schizophrenia, and if these risk factors are differentially related.

Chapter Two (‘*The relationship between environmental and polygenic risk for schizophrenia and cortical thickness in SFMH’)* investigated the impact of up to five individual environmental risk factors for schizophrenia on CT by means of analysis of covariance (ANCOVA) tests. Using PGRS-SCZ, the genetic association between schizophrenia and CT was also examined. Furthermore, the effects of environmental risk factors were controlled for PGRS-SCZ to determine if genetic and environmental impacts on schizophrenia are independent. As this was a case-control study, we were also able to test for differences between the two populations. Evidence was found to suggest that genetic and environmental risk factors did differentially impact CT across both patient and control groups. Such findings provide further evidence for a neurodevelopmental basis in schizophrenia. However, further investigation of these risk factors with other cortical structure metrics is needed.

Chapter Three ('*Exploring the causal relationship of birth weight on adult cortical brain structure in UK Biobank'*) examined the phenotype birth weight, as a proxy for obstetric complications (OC), to determine if this risk factor (with both genetic and environmental components) was related to three cortical measures; CV, CT and SA. Mixed linear models were employed to test for effects in both the whole birth weight in addition to a sub-set of individuals falling within the normal birth weight range. A different technique was used to assess the genetic component to this phenotype. Additionally, a Genome Wide Association Study (GWAS) was conducted in order to identify genetic variants associated with birth weight and a Mendelian Randomisation (MR) analysis was tested to determine if birth weight associated genetic variants were causally related to cortical structure. Findings indicate that subtle differences in birth weight may have long term effects on cortical structural development. This chapter also found evidence of a causal relationship between birth weight and brain structure in which lower birth weight (as indexed by genetic variants) is thought to cause lower CV and SA. This chapter highlights the neurodevelopmental impact that low birth weight could have in non-clinical populations and, as such, denotes a potential target for interventions that may help to prevent birth weight restrictions. However, further investigation into the specific impact of birth weight on cortical structure in the development of schizophrenia is required.

Chapter Four *('Impact of polygenic risk for Schizophrenia on cortical structure in UK Biobank')* aimed to replicate the findings from Chapter Two. Specifically, the association between PGRS-SCZ and cortical structure was examined in a larger, population-based sample. A replication of global CT was found, suggesting that genetic risk variants for schizophrenia are associated with CT. A trend towards a correlation between birth weight and PGRS-SCZ was also evident in this chapter however, as the correlation coefficient was so small (- .044) and the *p* value was only marginal (.069) despite the large sample size (*n* = 2,864), this result is not considered strong enough to infer shared genetic architecture between schizophrenia and birth weight. Additionally, tests were performed to test for an interaction between PGRS-SCZ and birth

weight on cortical structure and found no significant effects. Together these findings intimate that a higher genetic loading for schizophrenia is not related to birth weight and thus, again, do not support a shared effect of genetic variants for schizophrenia and birth weight on CT. Furthermore, in terms of interpreting the previous MR findings on the associations between birth weight and brain structure, it should be noted that potential genetic overlap between schizophrenia and birth weight does not violate the assumptions of MR and thus, these results should be considered separately. Chapter Four provided further evidence that genetic and environmental risk factors for schizophrenia may impact cortical structure differentially however, further investigation in to the relationship these factors have in relation to the development of schizophrenia is required.

Together, the findings presented within this thesis raise several interesting points.

Firstly, results suggest that polygenic and environmental risk factors for schizophrenia impact cortical structure, with stronger effects in individuals with the disorder compared to healthy controls. However, only a small amount of variance in these cortical abnormalities is explained by these effects, particularly in relation to PGRS-SCZ. Such results indicate that PGRSs may not have enough predictive accuracy for clinical utility but may be more useful when considered in conjunction with other risk factors (e.g. environmental factors or copy number variants) (Lewis and Vassos, 2017, Lawrie et al., 2011). However, despite the current effort to test for cortical associations with several environmental risk factors, many more factors remain in need of consideration (e.g. other OCs, additional childhood adversities) (Matheson et al., 2013, Schlosser et al., 2012, Matheson et al., 2011, Stilo and Murray, 2010, Dean and Murray, 2005, Mäki et al., 2005, Cannon et al., 2002b, Geddes and Lawrie, 1995). Nevertheless, this body of work provides evidence of an association between both genetic and environmental risk factors and alterations in cortical structure, highlighting potential mechanisms for their impact (e.g. synaptic pruning, myelination, neural stem cell proliferation) (Geoffroy et al., 2013, Lee et al., 2012). Furthermore, these results stress the importance of increasing public awareness of the link between these risk factors and schizophrenia development; particularly in relation to potentially modifiable environmental factors (Stepniak et al., 2014).

Secondly, Chapter Two evidenced a positive association between number of risk factors and cortical structure differences. However, chapters Three and Four suggest that, although birth weight variations are linked with cortical structure, differences in these variations are not associated and do not interact with the genetic liability for schizophrenia. Furthermore, previous studies have noted that whilst high incidences of these environmental risks are reported amongst individuals with schizophrenia, not all individuals who experience the same number and type of these factors go on to develop the disorder (Crush et al., 2018). As such, elucidation of resilience mechanisms or protective factors are required to better understand schizophrenia development (Radua et al., 2018, Bozikas and Parlapani, 2016, Schlosser et al., 2012).

Thirdly, these results may highlight how both small and large samples can be utilised in ways which are complimentary of each other. Monteith et al. (2015) asserted that data of all sizes are required in healthcare and that small samples still have an important role in research advancements. In the current thesis, a small sample (n < 50 per cohort), which provided deep, case-control phenotype data (Chapter Two), highlighted a potential pattern of associations between cortical structure and schizophrenia risk. Meanwhile, the large population-based data sets (n = ~2,000; tested in Chapters Three and Four) provided evidence of a replication of these effects which may be more generalisable. This approach allows for researchers to both make use of modest neuroimaging samples, which are generally more resource efficient and simpler to analyse (Monteith et al., 2015); as well as replicate important findings in much larger samples that are better equipped to detect smaller effects (Smith and Nichols, 2018).

5.2 Limitations

Limitations relating to each specific chapter have already been detailed therefore, outlined below are a number of general limitations applicable to the whole thesis.

5.2.1 Power Firstly, all studies contained within this thesis are limited by insufficient power resultant from small sample sizes. As a result, these studies may not be able to reliably detect environmental and genetic effects on cortical structure and thus, lack generalisability. Whilst the sample sizes used were considered to be, at least, moderate and normal (< 50) (Smith and Nichols, 2018), recent developments in neuroimaging technology and recruitment strategies have allowed the investigation of larger samples (Smith and Nichols, 2018, van Horn and Toga, 2014), especially with the advent of 'Big Data' (> 1,000 scans) (Smith and Nichols, 2018). Utilising 'Big Data' increases the probability of researchers detecting genetic variants that may be 'clinically actionable' (He et al., 2017) as well as small imaging effects (Smith and Nichols, 2018) that may not be measurable in smaller samples. Moreover, for GWAS and PGRS analyses, larger sample sizes are necessary to achieve the greatest accuracy (Dudbridge, 2013). The issue of power may underlie why some cortical structure associations were found in Chapter Four but not Chapter Two. However, in increasing sample sizes, the probability of detecting false positives also increases (Smith and Nichols, 2018). To overcome such caveats, it is important to use power analyses to calculate the minimum sample size required to detect effects with adequate power. Post-hoc power analyses pertaining to Chapters Two and Four are given in **Appendix D** (p97-99)**.**

5.2.2 Environmental Risk Factors Although efforts were made within this thesis to tease apart the differential effects of genetic and environmental risk factors for schizophrenia on cortical structure, our ability to do so was limited by the availability of phenotypic data. For example, the Scottish Family Mental Health (SFMH) data set used in Chapter Two contained data on five environmental risk factors for schizophrenia however, only three of these were available for control participants. This caveat, alongside small sample size, limited our ability to statistically analyse potential gene × environment (G × E) interactions. Furthermore, whilst the UKB dataset has a wide range of phenotypic data, it was not designed to investigate schizophrenia risk factors. As such, this thesis was constrained by limited data on adverse life events, urbanicity and migration, and complete lack of data relating to cannabis. Furthermore, due to limited clinical data within UKB, it was not possible to assess case-control differences.

Going forward, UKB aims to execute data linkage with National Health Services records which may supply mental health diagnosis information and thus, overcome some of the data limitations in the current body of work. Further work is therefore required to collect or identify more variables that can be linked to schizophrenia as well as different strategies to statistically analyse them (e.g. structural equation modelling).

5.2.3 Schizophrenia Onset/Development Associations between cortical structure and genetic and environmental risk factors for schizophrenia were evidenced in both a population-based and case-control sample. However, as schizophrenia is thought to typically develop in late adolescence or early adulthood (Gogtay et al., 2011) and the age range for the samples used in the current thesis was 18-67 years (SFMH) and 46-78 years (UKB), the relationship of these associations with schizophrenia development could not be investigated.

As birth weight and PGRS-SCZ are developmentally stable constructs, it is assumed that their associations with cortical structure would be evident earlier in life however, longitudinal assessments are required to confirm this as well as rule out potential brain ageing effects. Furthermore, testing for schizophrenia status (e.g. case-control/familial high-risk, duration of illness or severity of symptoms) would help elucidate whether these risk-associated cortical deficits are a result of the disorder or predate onset. Efforts were made to assess case-control differences in Chapter Two but were limited by sample size thus, use of large, prospective samples may be more beneficial.

5.3 Future Directions

In recent decades, an abundance of research has sought to investigate the aetiology, progression and prognosis of schizophrenia. Given the prevalence of the disorder (~ 1%) and its detrimental impact (Gogtay et al., 2011), it is of the upmost importance that we find more efficacious ways to diagnose the disorder earlier, and to develop better treatments and interventions (Häfner and Maurer, 2006, McGlashan, 1998, McGlashan and Johannessen, 1996). However, due to the heterogeneous nature of the disorder, it remains difficult to achieve

these aims. It is likely that with the continued use of 'Big Data' samples (e.g. UKB) and mega/meta-analytic approaches more opportunities will become available to fully explore the relationship between risk factors for schizophrenia and the detrimental impacts these can have, particularly on the brain. Some potential directions for this research are highlighted below.

1) First and foremost, future research should aim to replicate the results in the current thesis. We noted in the *limitations* section that larger sample sizes are required in order to increase the statistical power of our analyses (Smith and Nichols, 2018), particularly in relation to genetics based statistical methods such as PGRS (He et al., 2017, Palla and Dudbridge, 2015, Dudbridge, 2013). Furthermore, calculating required sample sizes would allow for more confidence in the accuracy and generalisability of the results for clinical application.

2) Another way in which schizophrenia-associated genetic variants can be used in order to determine intervention and prevention methods is through genetic pathway analysis (NPA-PGC, 2015). Rather than include variants across the whole genome to infer genetic risk (as in PGRS-SCZ), this method identifies a sub-set of genetic variants that are linked to distinct biological pathways and determines if they are implicated in the genetic aetiology of a disorder (NPA-PGC, 2015). Specifically, pathways linked with synapse and post-synapse related processes have been strongly associated with schizophrenia aetiology (NPA-PGC, 2015). Expanding on this information, it is possible to create a PGRS based on these pre-identified pathways and use this to test for associations with phenotypes of interest (e.g. Barbu et al., 2018). Thus, testing for an association between a PGRS for the identified pathways and CV, CT or SA would allow researchers to determine if these metrics are implicated in the manifestation of genetic risk for schizophrenia. Consequently, this would provide us with a mechanistic means for understanding disorder aetiology (Barbu et al., 2018).

3) More in-depth investigation of environmental risk factors and how they impact upon and interact with brain structure. As noted in Chapter One, many studies have found several environmental factors to be linked with an increased risk of developing schizophrenia (Murray et al., 2017, Lawrie et al., 2011, Matheson et al., 2011, Stilo and Murray, 2010, van Os et al., 2010, Dean and Murray, 2005, Mäki et al., 2005) and the current thesis has evidenced birth weight, as well as an accumulative experience of childhood adversity, OC, urbanicity, cannabis use and migration, to be linked with cortical structure. However, future research would benefit from developing an environmental risk score approach. To illustrate, a recent study created a 'polyenviromic' risk score using an approach similar to that used to devise PGRSs (Padmanabhan et al., 2017). Padmanabhan and colleagues (2017) found this score to be significantly correlated with transition to psychosis in high-risk subject; an approach that could be applied to cortical structure. However, this approach fails to consider genetic risk factors for schizophrenia. Furthermore, both this and the current environmental risk score approach fails to consider 'dose' effects of particular factors (e.g. cannabis) (Battistella et al., 2014) or the potential interactions they may have with each other (Padmanabhan et al., 2017, Neilson et al., 2017a (Chapter Two)); factors that should be addressed by future studies.

4) Future research would benefit from investigating modifiable environmental factors which could be used for mental health interventions. Many of the recognised modifiable risk factors relate to better prenatal care and in utero environment (Keskinen et al., 2016, Tiemeier et al., 2016, Hamlyn et al., 2013) with one study identifying better mental health of the mother, during this period, as a protective factor for schizophrenia (Keskinen et al., 2016). Thus, further research into OCs in particular, could be a fruitful endeavour.

5) It is also important to explore potential protective factors for schizophrenia (Keskinen et al., 2016, Schlosser et al., 2012,), resilience to it (Bozikas and Parlapani, 2016) and

their relationship with schizophrenia-associated cortical alterations. Protective factors could be environmental (Keskinen et al., 2016) or genetic (e.g. the mutant allele of FOS rs1063169 SNP) (Boyajyan et al., 2015) and both are worthy of investigation. Although previous studies have found an association between structural and functional brain imaging with resilience for Bipolar Disorder (Frangou, 2011), no such research has yet been conducted in schizophrenia. Whilst studies investigating resilience to schizophrenia are important, a lack of working definition for the construct presently inhibits such research (Luthar et al., 2000).

6) A further suggestion would be to employ longitudinal, prospective samples to investigate the link between environmental factors and cortical structure. Such research would enable the detection of factors that contribute to cortical structure deficits temporally related to schizophrenia onset, whilst ruling out potential ageing effects on the brain. This method would allow for more accurate detection of early risk factors and the development of early intervention strategies which would align with the aims of the 'Current Mental Health Strategy 2017-2027' for the Scottish Government (https://www.gov.scot/Publications/2017/03/1750/0) as well as add to the evidence base for the development of future policies.

7) Lastly, evidence suggests that the environmental risk factors for schizophrenia may also increase risk for other neurodevelopmental disorders. To illustrate, effects of variations in birth weight (and other OCs) on cortical structure have been found in a range of psychiatric and neurodevelopmental disorders (Buoli et al., 2016, Haukvik et al., 2014, Abel et al., 2010). In addition, intercranial volume has been associated with genetic risk variants for attention deficit hyperactivity and autism spectrum disorders (Lee et al., 2016). Hence, assessing associations between cortical structure and environmental risk factors using PGRS for a range of psychiatric disorders could be useful.

5.4 General Conclusions

In summation, this thesis outlined a collection of novel studies which attempted to disentangle the link between environmental and genetic risk factors for schizophrenia and cortical structure. Linear and mixed-method modelling, GWAS, and MR analyses were all employed to achieve this goal. Importantly, each chapter evidenced that both environmental and genetic risk factors associated with one or more cortical metrics. Furthermore, although the studies presented within this thesis suggest these factors impact upon the brain independently the role of G × E interactions could not be fully established. A limitation of this body of work pertains to the inability to determine at what point in the neurodevelopmental process these factors impact the brain or the direct relationship they have with schizophrenia development. However, finding evidence of links between schizophrenia risk factors and cortical structure provides us with an important building block upon which to determine the answers to these questions. Moreover, it has been recently suggested that the only way to improve clinical outcomes is to use early detection approaches, which consider complex models (incorporating all of the potential schizophrenia risk variables), integrated with clinical frameworks which highlight preventative interventions and are implemented by national health services (Fusar-Poli et al., 2017). Applying the techniques outlined in the current thesis, to larger, longitudinal, prospective samples, as well as developing a more thorough investigation into individual environmental risk factors for schizophrenia will be an important starting point in this endeavour. Future research thus has the potential to identify meaningful, modifiable environmental risk factors for interventions to be targeted towards and, potentially, slow or even prevent schizophrenia onset.

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